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Impact of Gene-Environment Interaction on the Real-World Expression of Psychosis Risk: Linking Genetic Variation, Childhood Adversity and Daily-Life Experiences across the Extended Psychosis Phenotype

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Linking Genetic Variation, Childhood Adversity and Daily-Life Experiences across the Extended Psychosis Phenotype

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"There is nothing either
good or bad
but thinking makes it so"

William Shakespeare

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CONTENTS

1. INTRODUCTION

Schizophrenia spectrum and other psychotic disorders are deemed the most disheartening forms of psychopathology, frequently associated with a profound personal distress and with substantial burdens and costs for the individuals and their family, but also for society as a whole (van Os & Kapur, 2009). Their lifetime prevalence is estimated at around 3% in the population (Perälä et al., 2007) and their onset often occurs in late adolescence or early adulthood, during or just after a sensitive period of structural and functional remodeling of the brain (particularly within limbic and cortical regions), as well as an intense period of personality, social and identity development (Eiland & Romeo, 2013)

Traditionally medical models have assumed a categorical view of disorders represented by diagnostic classification systems. According to these models, the spectrum of psychotic disorders, which comprises both affective and non-affective forms (i.e., schizophrenia-spectrum), has been characterized by the presence of abnormalities in one or more five domains of psychopathology (delusions, hallucinations, disorganized thinking, abnormal motor behavior and negative symptoms). However, contrary to the traditional categorical frameworks, compelling evidence has indicated that schizophrenia-related phenotypes are better expressed across a broad continuum of nonclinical (schizotypy traits, psychotic-like experiences), subclinical ("prodrome" or at risk mental states), and clinical (cluster A and psychotic disorder) manifestations with discontinuous degree of impairment and need for care (Kwapil & Barrantes-Vidal, 2015). Dimensional models based on the existence of a continuity between health and pathology provide a valuable opportunity for understanding symptom and disorder formation processes and for identifying critical targets for therapeutic interventions (Claridge, 1997). The work presented in this thesis is framed within this dimensional view, which considers that the extended psychosis

phenotype reflects not only a spectrum of similar phenotypes with an increasing degree of severity, but rather a phenotypic continuum reflecting a shared interactive set of multiple genetic-biological, psychological and sociocultural factors (Barrantes-Vidal, Grant & Kwapil, 2015; Debbané & Barrantes-Vidal, 2015). The most likely existence of a large number of causative factors, the wide developmental time period in which they operate and interact, and the existence of numerous moderating resilience factors seems to be consistent with the fact that the psychopathological space comprised between healthy individual differences in schizotypy personality traits and severe psychotic psychopathology is large; also there is evidence that there are dynamic developmental changes in the individuals' position along this hypothetic continuum of risk and resilience to psychosis.

Although the etiology of schizophrenia-related disorders is not entirely understood, converging evidence suggests that environmental and genetic factors are not only contributors, but also interact between them in several complex ways to produce vulnerability to phenotypic variance and disorder risk (Shah, Tandon, & Keshavan, 2013; van Os, Kenis, & Rutten, 2010; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005). Hence, the gene-environment interaction (G x E) approach is based on the synergistic co-participation between nature and nurture risk factors and, has been considered a remarkable approach for understanding the development of psychosis (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions, 2014; van Os, Rutten, & Poulton, 2008). In particular, the vulnerability-stress model of psychosis (Zubin & Spring, 1977), which posits that symptoms emerge when a threshold of stressors exceeds the individual's vulnerability level, has maintained a central position in the majority of contemporary theories. However, there has been a critical re-reading of the vulnerability-stress model in the last years. For a long period of time it had been assumed that the

diathesis or vulnerability for the psychosis phenotype was strictly caused by genetic factors, whereas environmental components acted as mere 'triggers' of this biological susceptibility (Read & Bentall, 2012; Read, van Os, Morrison, & Ross, 2005). In recent years, this notion has been reconsidered in light of impressive advances of affective and social neuroscience showing how environmental exposures impact on brain's structure and function, being thus, active agents in the formation of an individuals' level of vulnerability. Therefore, the thesis is embedded in a current zeitgeist of an exciting reframing of our dogmatic dualism when considering notions such as nature-nurture, brain-mind and gene-environment.

A fast-growing field of epidemiological research has recently showed an association of psychosocial environmental factors in the vulnerability towards psychotic phenomena (Bentall & Fernyhough, 2008; Brown, 2011). Notably, the exposure to childhood interpersonal adversity has been linked to psychotic features in clinical and nonclinical populations (e.g. Varese et al., 2012). Similarly, it has been shown that daily life stressors have also a relevant impact in the expression of symptoms across the extended psychosis phenotype (Barrantes-Vidal, Chun, Myin-Germeys, & Kwapil, 2013; Myin-Germeys, & van Os, 2007). In this regard, Experience Sampling Methodology (ESM) has allow to examine the experience and expression of psychological constructs as well as contextual factors (e.g. momentary stress) in real-life settings (Oorschot, Kwapil, Delespaul, & Myin-Germeys, 2009). Importantly, it has been indicated that the use of prospective and repeated assessment with ecological validity improves the precision, reliability and quality of GxE research (Moffit, Caspi & Rutter, 2005) and, adds the traditionally scarce value of ecological validity to psychopathological research. Thus, ESM studies have been able to provide insight on mechanisms underlying of the extended psychosis phenotype (e.g., Myin-Germeys, Oorschot, Collip, Lataster, Delespaul, & van Os, 2009).

Among the most relevant mechanistic process implicated in psychotic phenomena (e.g., distortion of cognitive schemas, attachment style, social identity, etc.), it has been hypothesized that childhood interpersonal adversity may increase the risk for psychotic features through a process of behavioral and biological sensitization (van Winkel, van Nierop, Myin-Germeys, & van Os, 2013). A number of single nucleotide polymorphisms (SNPs) have also been examined as moderators of environmental factors due to their functional impact on relevant individual differences implicated in biological stress-regulation systems. The empirical studies conducted as part of this thesis are embedded in a larger longitudinal project (PSYRIS-Barcelona; Barrantes-Vidal, Chun, Myin-Germeys, & Kwapil, 2013a; Barrantes-Vidal et al., 2013b; Sheinbaum et al., 2015) investigating with ecological validity the intricate GxE interplay across the extended psychosis phenotype (including participants with individual differences in schizotypy, at risk mental states and first episode psychosis). In particular, the work carried out in the current thesis had the primary goal of shedding new light on the ways in which gene and environmental factors interact to psychosis risk expression in daily life, thus contributing to our understanding of the relevant mechanistic pathways leading to the extended psychosis phenotype.

Another aspect dealt with in this thesis has been the recent interest in overcoming the traditional restrictive definition of environmental factors from a negative standpoint, especially so in psychosis research. Indeed, the notion of vulnerability as a pre-dispositional factor to psychopathology (Ingram & Luxton, 2005) has led to a predominant focus on the assessment of adversities, neglecting positive experiences. Alternative recent models of GxE interaction drawing from developmental psychopathology such as the differential-susceptibility to environment hypothesis (Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011) have underscored the biasing emphasis of GxE interaction on environmental

adversities, posing that individuals differ on the degree in which they are affected by the *whole* environmental spectrum (from positive to negative). Understanding how individuals respond to both sides of environmental influences is essential for disentangling resilience processes and thereby obtain a complete and thus adequate characterization of the etiology of mental disorders. Altogether, the findings of this thesis intend to yield findings that may ultimately have implications for identifying not only risk but also resilience key targets for prophylactic interventions.

2. THEORETICAL BACKGROUND

2.1. The Continuum Hypothesis or an Extended Psychosis Phenotype

A large body of literature has consistently showed that the psychosis phenotype is expressed across a dynamic continuum which ranges from nonclinical (e.g., schizotypy, psychotic-like experiences), subclinical (e.g., at risk mental states for psychosis) to a range of full-blown clinical manifestations (schizotypal personality disorder, brief psychosis, schizophreniform disorder, schizophrenia, delusional disorder and psychotic affective disorders; Claridge, 1997; Kwapil & Barrantes-Vidal, 2015; Kwapil, Barrantes-Vidal, & Silvia, 2008; Meehl, 1990). Increasingly evidence has indicated that milder forms of psychotic symptoms are also present in individuals from the general population (Kaymaz & van Os, 2010). However, only a small proportion of these psychotic experiences may become persistent over time and eventually result in the development of a psychotic disorder (Kelleher & Cannon, 2011; Linscott & van Os, 2013; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Elucidation of the processes involved in the extension of this phenotypic continuum is essential for the identification of individuals possessing liability to psychosis and for the examination of the role of environmental and genetic factors in the make-up of the vulnerability to schizophrenia and other psychotic disorders (van Os & Reininghaus, 2016)

The continuum or dimensional hypothesis of psychosis, which derives from the classic notions of Kretschmer, poses that schizotypy and schizophrenia are not, qualitatively distinct or separate entities, but rather the same etiological and developmental processesare hypotheseised to underlie the phenomenological similarity with varying degrees of severity and dysfunctionacross nonclinical and clinical manifestations (Barrantes-Vidal et al., 2015). Naturally, as many

etiological factors are at play and operate at different developmental timings and in different combinations, a large spectrum of phenomenological expression would be yielded (Claridge, 1997). In contrast, users of the expression 'extended psychosis phenotype' tend to be "agnostic" as to whether there is continuity in terms of etiological factors.

Both schizotypy and schizophrenia are contemplated as multidimensional constructs (Raine et al., 1994; Stefanis et al., 2004; Vollema & van den Bosch, 1995), where positive, negative and disorganized symptom dimensions are the most consistently identified (Kwapil, Barrantes-Vidal, & Silvia, 2008). The positive or psychotic-like dimension is characterized by features that reflect distortion or excess in normal functions as unusual perceptual experience and odd beliefs. In contrast, the negative or deficit-like dimension encompasses different functional impairment features, such as anergia, anhedonia, affective flattening, avolition, asociality and alogia. Lastly, the disorganized dimension is characterized by disorganized behavior and disturbances in the organization and expression of thought and affect (Kwapil & Barrantes-Vidal, 2015).

Research on the multidimensional structure of the schizotypy has demonstrated that the dimensions are associated with differential patterns of symptoms and impairment in cross-sectional studies using both questionnaires and interview methods (e.g., Barrantes-Vidal et al., 2013b; Barrantes-Vidal, Ros-Morente, & Kwapil, 2009) and importantly, in studies using momentary assessments (e.g., Kwapil, Brown, Silvia, Myin-Germeys, & Barrantes-Vidal, 2012). For instance, one study revealed that positive and negative schizotypy exhibit differences in the real-world expression of symptoms, affect, social contact, social functioning and stress reactivity in nonclinical sample of young adults (Barrantes-Vidal et al., 2013a). Furthermore, the schizotypy

dimensions have been found to predict the development of schizophrenia-spectrum disorders in prospective interview studies (Kwapil, Gross, Silva & Barrantes-Vidal, 2013).

Cross-sectional and longitudinal studies of patients with psychosis have greatly informed our understanding of the phenomenology of psychotic disorders, but are ultimately limited in their potential for investigating the development, expression, and prevention of psychosis. Conversely, the construct of schizotypy provides a useful framework for the assessment of etiological factors without the confounding effect of factors associated to clinical status and enhances the identification of protective and resilience mechanisms involved in psychotic phenomena (Barrantes-Vidal et al., 2015). Overall, it seems that the identification of etiological factors across the extended psychosis phenotype continuum may provide critical insights into etiology and offer great opportunities for prevention and treatment.

2.2. From Chronicity to Prevention: Early Detection and Intervention in Psychosis

During the last century, the predominant diagnostic system for psychotic disorders has been based on factitious divisions of cross-sectional groups of symptoms, and has focused on course and outcome variables. This approach disregards the onset of disorder, since as it cannot provide a differentiation between early clinical features and characteristics of persistent disorder (McGorry, Nelson, Goldstone & Yung, 2010). Consequentially, for over a century, a damaging combination of pessimism, stigma and neglect have constrained therapeutic advances (Mcgorry, Killackey & Yung, 2008). Nonetheless, in the last decades, a large body of research has undergone a paradigm shift towards the identification of early stages of mental disorders and preventive intervention, including increased focus on “prodromal” or “at risk mental states” for psychosis

(ARMS) and first episode psychosis (FEP) individuals. In this regard, the clinical staginge model has shown proofed particularly useful for the distinction between early subclinical phenomena and those features that accompany severe clinical course and chronicity (McGorry et al., 2010).

Furthermore, taking into consideration that neurodevelopmental theories of psychosis (e.g., Murray & Lewis, 1987; Weinberger; 1987) which assume that etiopathogenic factors are expressed during the prepsychotic phase, the early detection and prospective evaluation of ARMS individuals have been considered critical for identifying biological, social, and psychological vulnerability factors implicated in the development of the psychotic disorders. From a therapeutic standpoint, understanding the development of psychosis is crucial for identifying targets for future interventions (Cornblatt et al., 2003) and, importantly, for minimizing the chronic course and mortality associated with psychosis (McGorry et al., 2009). Thus, a focus on prevention in prodromal or subpsychotic and even nonpsychotic individuals promises the possibility of forestalling or minimizing the emergence and course of psychosis.

The detection of at-risk individuals has typically followed two approaches: i) the basic symptom approach, based on self-reported subclinical disturbances in thought, speech, and perception and, ii) the ultra high-risk approach, based upon attenuated or intermittent positive symptoms of psychosis. Although, the ultrahigh-risk approach has predominated because it is presumably closer in severity to clinical disorders (Cannon et al., 2008), the basic symptoms approach has also proved useful for even earlier detection of risk (Schultze-Lutter et al., 2008). Importantly, in order to identify an early risk of psychosis, these two approaches are increasingly combined in current studies (Klosterkötter, Schultze-Lutter, Bechdolf y Ruhrmann, 2011). Conversely, there is no consensus in the operational definition of FEP individuals and diagnostic systems (e.g., DSM-V; American Psychiatric Association, 2013), which only provide a little

guidance for FEP characterization. Therefore, despite the establishment of successful clinical research programs focused on early detection and intervention in psychosis, further studies are still needed in order to provide a better characterization of the early phases of psychosis with the purpose of improving early detection and reaching a valid cross-cultural definition in both ARMS and FEP individuals (Domínguez-Martínez, Cristóbal-Narváez, Barrantes-Vidal, & Kwapil, in press). Furthermore, given the complex etiology and heterogeneous clinical manifestation of psychosis, there is a great need for studies that examine the role of the relevant psychological mechanisms involved in the real-world expressions of psychotic symptoms in both high-risk and FEP individuals.

2.3. Etiological Factors in the Psychosis Continuum

Causative models of psychosis continue to be incomplete and there are multiple views regarding one of the most complex challenges in psychopathology science. One of the most common accepted frameworks continues to be the neurodevelopmental hypothesis, which postulates that both pre and postnatal environmental factors interact with genetic vulnerability to yield different pathophysiologic processes that impair brain development (e.g., Cannon et al., 2003; Murray & Lewis, 1987; Weinberger, 1987) and produce a broad range of risk trajectories, endophenotypes (intermediate phenotypes) and phenotypic expressions (Weiser, Davidson, & Noy, 2005).

Along with the longstanding genetic-biological conceptualization of psychosis, stress has been an enduring factor in models and theories of the etiology of psychosis (Holtzman et al., 2013). The vulnerability-stress model (or diathesis-stress) model of psychosis (Zubin & Spring, 1977), which posits an interplay between individual's vulnerability level and stress, has been widely

accepted as an etiological framework for the study of the causes and clinical course of schizophrenia-related disorders. Variation in this vulnerability level has been shown to be related so far to genetic factors and, more recently, to environmental insults.

2.3.1. Genetic Factors (G): Single Nucleotide Polymorphisms (SNPs)

During the last two decades, psychiatric genetics research has attempted to identify the genetic variation underlying psychosis risk. The first attempt was linkage analysis, which consists in the location of those genetic markers (variants of DNA sequence) that co-occur with the presence of a disorder in pedigreed families with both affected and unaffected individuals (Manuck & McCaffery, 2014). Although the approach is characterized by a lack of theoretical connection with the disorder, it has been useful for determining chromosomal regions associated with single genes disorders (e.g. Huntington disorder). However, it has failed to identify genetic variants in complex disorders (e.g. major depression, schizophrenia, bipolar disorder, etc.), where the small effect of many genes - that is, a polygenic model of inheritance - contributes to the development of the disease (Risch & Merikangas, 1996).

A second method was the candidate gene approach, which had already been applied for a number of years. Contrary to the absence of hypothesis-driven of linkage analysis, candidate gene studies aim at targeting those risk alleles of gene polymorphisms, that for their relevant functional variation, are associated with the risk outcome. One example is the single nucleotide polymorphism (SNP) *COMTVal158Met*, which involves a nucleotide substitution from guanine (G) to adenine (A) at codon 158, that results in an amino acid change from Val to Met, leading to alteration of *COMT* enzyme activity (Lotta et al., 1995). Recently, candidate gene studies, have

also sought to identify haplotypes – that is, combination of alleles of several polymorphisms within the same gene (e.g., *FKBP5* haplotype).

More recently, sophisticated molecular strategies such as genome-wide association study (GWA) have been used. These techniques exhibit some features of previous linkage and candidate genes approaches. For instance, they are hypothesis-free but also capable of detecting the small effects of genetic variants. Importantly, taking into consideration the strong disequilibrium linkage between genes, these techniques genotype only few variants and predict the others with a high degree of accuracy. Ultimately, the new copy number variants (CNVs) approach has extended previous findings identified by GWAS (e.g., Grozeva et al., 2010). However, despite of technical advances, the total common variants detected in these studies only explain a small proportion of heritable differences among individuals, giving rise to the scientific debate of the "missing heritability" (Maher, 2008). Therefore, it seems that genetic research based on the direct association between genes and psychotic disorders (and, importantly with few or no measures of environmental exposures) has failed to make any substantive progress (van Os et al., 2008).

2.3.2. Environmental (E) Factors: the Role of Psychosocial Stress

Conversely, convergent epidemiological evidence has shown an association of psychosocial factors both at macro (e.g. urbanicity, poverty, minority status) and micro (e.g. family environment, childhood adversity) levels with schizotypy traits, subclinical and clinical expressions of the psychotic phenomena (Bentall & Fernyhough, 2008; Brown 2011). Accordingly, renewed attention has been focused on the contribution of psychosocial adversity to the etiology and course of schizophrenia and spectrum disorders over the last decade (van Os & Kapur, 2009).

Among the most relevant macro-environmental risk factors, some studies have reported that people in a urban environment is more likely to endorse psychotic experiences compared to those in a rural surrounding (e.g. Krabbendam & van Os, 2005; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006). Similarly, socio-economic difficulties have been associated with an increased risk of reporting psychotic experiences across the extended psychosis phenotype (e.g. Saha, Scott, Varghese, & McGrath, 2013). In addition, it has also been shown that migrant status is associated with a higher prevalence of psychotic experiences (van Os et al., 2009). Importantly, it has been suggested that it is not merely the migration situation, but rather are the specific features of the host social context (e.g. being in a minority group) that are more likely to elevate psychotic experiences levels in immigrants individuals (van Os, 2012).

Several studies have also shown a relevant link between micro-environmental risk factors and the risk and course of psychotic disorders (Sheinbaum & Barrantes, 2015). For instance, certain features of the family milieu (e.g., negative expressed emotion) have been associated with PEs (Polanczyk et al., 2010). Evidence has also shown that childhood interpersonal adversities are more likely to endorse psychotic experiences in clinical and non-clinical populations (Varese et al., 2012). The present thesis focuses on the impact of this micro-environmental risk factor on psychotic phenomena.

2.3.2.1. The Case of Childhood Interpersonal Adversity

A fast-growing research has recently pointed to the role of particular adverse early-life stressors in the emergence of specific symptoms domains. The impetus of this research is the refinement of etiological models of psychosis vulnerability and the identification of key targets for prophylactic intervention among individuals exposed to childhood adversity.

The term "childhood adversity" encompasses a broad range of forms of adversity in childhood, including abuse (sexual, emotional and physical), neglect (emotional and physical), bullying victimization and non-interpersonal events (e.g. accidents). Although some studies are conflicting (e.g., Alemany et al., 2013; DeRosse, Nitzburg, Kompancaril, & Malhotra, 2014), the general consensus suggests that childhood adversities are more strongly associated with the positive dimension of reality distortion than with negative or disorganized dimensions (e.g. McCabe, Maloney, Stain, Loughland, & Carr, 2012; Ruby et al., 2014; Velikonja, Fisher, Mason & Johnson, 2015). In addition, evidence suggests that experiences characterized by an intentional nature (e.g. abuse, neglect, bullying) are also more robust associated with psychotic features than those without intent (e.g., Arseneault et al., 2011; van Nierop et al., 2014a).

The binding constraint on the assessment of adverse experiences has been the use of crude measurements, such as checklists with open-ended questions that require dichotomous responses (e.g., yes or no; Fisher & Craig, 2008; Velikonja et al., 2015). In addition, another limitation of much epidemiological research is that trauma measures may not able to capture more subtle forms of interpersonal adversity, which can also have detrimental effects on psychological functioning. Some review studies (e.g., Bendall, Jackson, Hulbert, & McGorry, 2008) have suggested the use of validated trauma measures, which include questioning about objective information, such as the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998), the Traumatic events in Childhood (ITEC; Lobbestael, Arntz, Harkena-Schouten & Bernstein, 2009) and the Childhood Experience of Care and Abuse (CECA; Bifulco, Brown, & Harris, 1994). These have been the measures used in the studies presented in the current thesis.

2.3.2.2. Measurement of Adversity in Daily Life: Momentary Stress and Experience Sampling Methodology (ESM)

In light of previous epidemiological findings linking psychosocial stress with PEs, some studies have broadened the field by examining the impact of minor stressors or daily hassles on psychotic phenomena. In this regard, the transactional model of stress has suggested that individual appraisals about stressful events have a marked impact on health and functioning outcomes (DeLongis, Coyne, Dakof, Folkman, & Lazarus, 1982; Folkman & Lazarus, 1985; Lazarus & Folkman, 1984). Additionally, it has also been indicated that as time goes by, individuals tend to make disproportionate emphasis on certain events, while minimizing the effects of others. Thus, many studies have focused on the notion of stress, conceptualized as the subjective appraisal of stressfulness about distinctive events and minor disturbances in the natural flow of daily life (Myin-Germeys & van Os, 2007). Notably, these studies have shown that the appraisals of daily life stressors play an important role in schizotypy traits, subclinical and clinical expressions (e.g., Barrantes-Vidal et al., 2013; Myin-Germeys & van Os, 2007). Taken together, the subjective approach assessing the amount of perceived stress has traditionally been chosen over an objective approach assessing the objective occurrences of events. In this sense, it has been indicated that similar amounts of objective stress may cause more subjective stress in patients with schizophrenia (Lukoff, Snyder, Ventura, & Nuechterlein, 1984).

Accordingly, researchers have increasingly employed the Experience Sampling Method (ESM) to examine the impact of stressful experiences on the expression of psychological constructs in daily-life (e.g., Oorschot et al., 2009; Mehl & Conner, 2012). ESM is a structured diary technique in which individuals are prompted randomly throughout the day in real-time and

in real-life. Thus, they can report their current experiences, such as emotional states, cognitions, and symptoms. This approach has provided several advantages compared to traditional assessment procedures, including enhanced ecological validity, minimization of retrospective bias, the possibility of assessing the context of experiences and the implementation of sophisticated multilevel regression analyses (e.g., Conner, Tennen, Fleeson, & Barrett, 2009; deVries, Delespaul, & Dijkman-Caes, 1992; Hektner, Schmidt & Csikszentmihalyi, 2006).

Notably, ESM has been able to capture the interactional nature of the vulnerability-stress model by analyzing dynamic person-environment interactions. Variability over time and dynamic patterns of reactivity to the environment have been considered as essential features of psychopathological experiences that need to be captured for a better understanding of the phenomenology and underlying mechanisms (Myin-Germeys et al., 2009). Furthermore, it has been also shown to be a useful tool for examining the clinical and subclinical expressions of the schizophrenia spectrum (e.g., Lataster, Valmaggia, Lardinois, van Os, & Myin-Germeys, 2013) and, given that it captures the phenomenology of symptoms as they unfold in the real world, it may complement current efforts to clarify links between adversity and psychosis symptoms.

2.3.2.3. Plausible Mechanisms Linking Stress and Psychosis:

Although the adversity—psychosis link is consistently associated with clinical and nonclinical manifestations of the psychotic phenomena, there is a lack of complete understanding about the underlying mechanisms involved. It is important to highlight that several mechanisms may act at different levels and interact in multiple dynamic ways increasing the risk for psychosis. For instance, recent and scarce literature has shown that psychological mechanisms (e.g., negative cognitive schemas, insecure attachment styles, and marked difficulties in social cognition) are

relevant interrelated processes involved in the developmental pathway from adversity to psychosis (Sheinbaum & Barrantes-Vidal, 2015). In particular, preliminary evidence has shown that the association between early childhood trauma and symptoms may depend on individual differences in attachment styles -that is, the way in which, though their early caregivers, children form internal working models and adquire affect regulation strategies (Sheinbaum, Kwapil & Barrantes-Vidal, 2014). Importantly, few studies have also studied the impact of distal factors (e.g., early childhood trauma, early attachment) with proximal factors (daily life stress) in the increased risk of psychotic features (e.g., Lardinois, Lataster, Mengelers, van Os & Myin-Germeys, 2011; Sheinbaum et al., 2015). Therefore, it is seemed that the field has much to gain by investigating the complex interplay of psychosocial factors involved on the psychotic phenomena. And so that inspirit, the present thesis has examined the interplay of some of the putative risk factors implicated in the extentend psychosis phenotype.

Another relevant issue that remains unsettled is whether adversity may be the cause or the consecuence of psychosis, given that a statistical association not necessary imply a cause role between adversity and symptoms. In this regard, even though there is still an intense debate in the field and more studies are needed to conclude causation, contemporary models seem to support a causal role of the adversity in the development of schizophrenia-related disorders (Barrantes-Vidal, 2014; van Winkel, et al., 2013).

2.3.2.3.1. The Traumagenic Neurodevelopment Model and the Stress Sensitization Hypothesis

The putative causal role of adverse experiences in the development of psychotic phenomena has been driven by a consistent body of research linking the neurobiology of childhood trauma with the brain structural and functional alterations in the schizophrenia-related disorders.

Based on this evidence, the traumagenic neurodevelopment model of psychosis poses that the prolonged or severe early-life adversity exposure in critical developmental periods (i.e., childhood) disrupt psychobiological stress regulation mechanisms increasing, therefore, the individual liability for the onset and, persistence of psychotic symptoms after re-exposition to stressful events (Read, Fosse, Moskowitz, & Perry, 2014). Support for this model comes from the evidence of animal and humans studies indicating that the early-life stress is associated with increased hypothalamic-pituitary-adrenal (HPA) axis responses and with striatal dopamine activation to later life stress (Heim et al., 2000; Liu et al., 1997; Pruessner, Champagne, Meaney, & Dagher, 2004). This is also consistent with the initial conception of the stress-vulnerability model of schizophrenia, which hold that stress susceptibility is not only inherited but could be acquired through the developmental experience on life history and behavior. Hence, from this perspective, the environmental stressors are not merely triggers of genetic liability, but rather are co-participating factors in the make-up of the vulnerability to psychotic features.

Several ESM studies have now demonstrated that the exposure to psychosocial adversity increases emotional and psychotic reactions to minor stressors in daily life in clinical populations (Myin-Germeys, Marcelis, Krabbendam, Delespaul, & van Os, 2005; Myin-Germeys, & van Os, 2007; Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001). Interestingly, stress reactivity has been found to be unrelated to neurocognitive impairment, suggesting the presence of different (stress vs non-stress related) pathways to psychosis. Whereas the stress reactivity pathway - also known as affective pathway to psychosis -is characterized by a predominance of positive symptoms, the neurocognitive dysfunction may be more characteristic of psychosis involving negative symptoms or poor prognosis (Myin-Germeys & van Os, 2007). Consistent with the notion that stress-sensitivity hypothesis would be a relevant pathway specifically for reality distortion,

one study shown that both momentary and social stress were associated with PEs and paranoia for those high in positive schizotypy and the experience of stress temporally preceded the onset of psychotic experiences only for those with high positive schizotypy, emphasizing the relevance of stress reactivity also on psychosis proneness (Barrantes et al., 2013a).

Collectively, the evidence that psychosis is associated with early-life adversity exposure and also with a greater reactivity to stress, has helped forge the concept of *behavioral sensitization*. This has been conceptualized as the process whereby repeated exposure to psychosocial stress may progressively increase the behavioral and biological response to subsequent exposures (van Winkel et al., 2008a). According to this, it has been suggested that exposure to early-life stress may increase emotional and psychotic reactions to small stressors in daily life. The studies presented in the thesis aim to investigate the putative role of stress-reactivity mechanism on the real-world expression of psychosis risk.

It has been hypothesized that the neurobiological substrate of sensitization may involve may increase the risk for psychosis through a process of behavioral and biological sensitization involving hypothalamus-pituitary-adrenal (HPA) axis dysregulation and contributing to a final common pathway of dopamine sensitization in mesolimbic regions (van Winkel et al., 2008a). In this regard, the mesolimbic dopaminergic system has considered a critical component in the attribution of salience, a process whereby events and thoughts are motivationally invested and influence goal-directed behavior due to their association with reward or punishment (Berridge & Robinson, 1998). It has been suggested that hyperdopaminergia, which has been long associated with reality distortion, may alter the attribution of emotional or incentive salience to both internal representations and external stimuli, which would lead to perceptual and cognitive distortions characteristic of psychosis (Kapur, 2003; Howes & Kapur, 2009).

2.3.2.3.2. Social Defeat Hypothesis

The social defeat (SD) hypothesis postulates that prolonged exposure to the experience of social defeat or social exclusion –that is, a negative experience of *being excluded from the majority group*- may lead to sensitization of the mesolimbic dopaminergic system and thereby resulting in a greater vulnerability for developing psychosis. The hypothesis proposes that SD is the unifying mechanism linking the major psychosocial risk factors (e.g. migration, childhood trauma) with the psychosis phenotype (Selten, van der Ven, E., Rutten, & Cantor-Graae, 2013). Interestingly, it has been suggested that the intentionality of harm of some childhood adversities (e.g., sexual, physical and psychological abuse, and bullying) putatively leads to feelings of outsider status and decreased self-value. However, the SD is not necessarily involved in those adversities of a non-intentional nature (e.g., accidents; Selten et al., 2013).

Consistent with the SD hypothesis, preliminary evidence has shown that SD (operationalized as feeling of worthlessness, hopelessness and self-devaluation) as well as affective dysregulation, mediated the association between childhood trauma and psychotic experiences (van Nierop et al., 2014b). Interestingly, SD uniquely explained the association between trauma and symptoms in the subgroup of individuals with psychotic disorders suggesting that SD may be more crucially involved in the trajectory leading to core clinical psychosis (van Nierop et al., 2014b). In relation to the biological aspects of the SD hypothesis, converging evidence from animal models suggests that, indeed, SD leads to sensitization of mesolimbic dopaminergic system (Hammels et al., 2015), whereas the evidence in humans is still scarce.

2.3.3. Ecogenetics: Evidence for Gene – Environment Interaction (GxE)

Despite of the intense confrontation between nature and nuture approaches over the last decades, compelling evidence has consistently showned that environmental factors are implicated in the etiology of schizophrenia-spectrum disorders. Moreover, given the substantial heterogeneity among individuals (not all individuals exposed to environmental risk or carrying genetic risk variants develop a disorder), it seems reasonable to expect some interaction between both genetic and environmental factors (Moffit, et al., 2005; van Os, et al., 2008). In psychiatry research, the term of "ecogenetics" was introduced to understand the complex ways in which nature and nuture interact increasing risk for a psychotic disease (Motulsky, 1977). From this ecogenetic framework, several types of GxE interactions have been relevant for the examination of complex disorders, providing evidence that both factors may coparticipate in different biological mechanisms increasing the risk for psychotic outcomes (Kendler & Eaves, 1986). In particular, the GxE approach holds that in the interaction between genes and environment, the effect of one factor (either genetic or environmental) is conditional on the other (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions, 2008).

The GxE research is still an emerging discipline, and importantly, conceptual and pragmatic questions have been raised on how to conduct and interpret the GxE research in psychotic disorders (Zammit, Lewis, Dalman, & Allebeck, 2010). For instance, a critical issue has been that the optimal sample size required to detect GxE interactions will vary according to the design used. Classical case-control studies require very large samples size because the genetic effects are expected to be small. However, large sample sizes are not always possible due to its own nature. Indeed, sample size requirements can be substantially reduced with high-quality measurement of environmental risk factors, especially when measures are repeated over time

(Wong, Day, Luan, Chan, & Wareham, 2003). In this regard, the use of momentary assessment technologies with many repeated measures holds promise for the detection of subtle interactions of genes and environments (Wichers, 2014).

Indeed, ESM is especially suited for GxE studies given that the phenotype (e.g., stress reactivity), is composed of multiple measurements with a close link to biological systems. Although an increasing number of GxE studies have used quantitative genetic epidemiology methods (e.g, twins and adoption designs) or genetic candidate GxE studies for the etiology of psychosis, few studies have investigated the role of GxE interaction on psychosis expression using momentary assessment methods. For instance, van Winkel et al. (2008b) showed that the *COMTVal158Met* polymorphism moderated the affective and psychotic responses to stress in patients with psychosis. Patients with the Met/Met genotype showed the largest increases in psychotic experiences and negative affect in reaction to stress assessed in daily life, providing evidence for GxE interaction mechanisms in the formation of psychotic symptoms. This study opened up a new and promising strategy for studying other candidate genes thought to be key in the regulation of stress and psychosis. This is the case, for instance, of the functional polymorphism Val66Met on the brain-derived neurotrophic factor *(BDNF*) gene, which has critically involved in neuronal development, differentiation and plasticity processes (Notaras, Hill, & van den Buuse, 2015). Similarly, genetic variation involved in the regulation of stress response system such as the FK506 binding protein 5 (*FKBP5*) gene has also received particular attention. Studies investigating these genetic variants in interaction with stressors in psychosis expression are still relatively rare, although this field has taken momentum in the last few years. The study of GxE interactions focused on these relevant SNPs in the field have been proposed in this thesis. In particular, this

work examines some SNPs related to psychosis pathophysiology and, some recently highlighted interesting genes in the context of the stress-sensitivity hypothesis that frames this proposal.

Finally, it is worth noting that GxE research has been almost exclusively guided by the lens of the diathesis-stress model (Gottesman & Shields, 1967; Monroe & Simons, 1991; Zuckerman, 1999), which establishes that individuals carrying genetic-risk are more vulnerable to the effect of environmental adversity and thus more prone to develop psychopathology. Therefore, the GxE approach has predominantly focused on the assessment of the *negative* side of the environment (adversity) and has almost disregarded the *positive* side (positive experiences). Conversely, the recent differential-susceptibility hypothesis (Belsky, & Pluess, 2009) has postulated that, due to evolutionary reasons, individuals with different genetic background may differ on the degree in which they are affected by the whole environmental spectrum (from positive to negative) and not only by the degree in which they are affected by adverse environments. Therefore, more plastic individuals are expected to be more susceptible to negative environments but also to positive environments. The present thesis examines whether genetic variation that entails individual differences in biological functionality may be risky or advantageous in positive and negative environments across the extended psychosis phenotype.

3. AIMS AND OUTLINE OF THE THESIS

The general aim of this thesis was to examine with ecological validity the impact of environmental factors (both distal and proximal) in interaction with genetic variation on the real-world expression of psychosis risk. Subsumed under this overarching goal, the present thesis sought to address issues related to:

(1) The interaction of both distal (interpersonal childhood trauma) and proximal factors (current momentary stress) on psychotic experiences in daily life;

(2) The role of the interaction of environmental factors with genetic variants relevant for stress-regulation mechanisms on the expression of momentary psychotic experiences;

(3) The moderating role of specific gene variants on the interplay of distal and proximal environmental stress factors, that is, the genetic moderation of potential stress-sensitization mechanisms impacting psychosis expression; and

(4) The plausible *protective* role of proximal (momentary) positive contextual factors and psychological appraisals in interaction with genetic variation on the expression of psychotic experiences in the realm of daily life. These aims led to the following research, which is divided into four main sections:

The first section, ***The synergy of distal and proximal environmental factors on psychosis risk expression,*** is dedicated to examine the joint contribution of distal and proximal adverse environmental factors on psychotic phenomena as well as some of the plausible mechanisms involved underlying their association. ***Chapter 1*** presents a study on the impact of a broad range of adverse childhood experiences on momentary real-life experiences and stress reactivity in a nonclinical sample of young adults characterized by a wide distribution of schizotypy traits and

psychotic-like experiences (i.e., with ample variability in terms of psychosis liability). This work adds to the extant literature in that it refines our understanding of how the impact of a variety of childhood adversity subtypes is expressed in *real life* and how these adversity subtypes are moderating affective and symptomatic reactivity to different forms of momentary stress. The study also covers the examination of the consistency across interview and self-report measures of abuse and neglect experiences in the association with psychotic experiences. It was hypothesized that childhood adversities would be more consistently associated with psychotic-like and paranoid experiences than with negative-like (alogia and blunted affect) features. In addition, it was expected that experiences characterized by an intentional nature (interpersonal abuse, neglect and bullying) would also be more robustly associated with psychotic features than those of a non-intentional nature (losses) or those occurring outside the relational domain (general traumatic events). It was also hypothesized that interpersonal forms of adversity would be relevant in moderating reactivity to both situational and social stress, whereas general traumatic events would be relevant in moderating reactivity to situational stress. Furthermore, it was expected that both interview and self-report measures for the assessment of abuse and neglect would show associations with daily life experiences; however, it was also expected that more differentiated patterns of associations would emerge with interview methods characterized for more objective and precise definitions of adversity.

The second section of the thesis, ***Gene-environment interaction on the real-life expression of psychotic experiences,*** is dedicated to examine the role of the interaction of genes and environments on real-world psychosis risk expression across the extended psychosis phenotype. The study presented in ***Chapter 2*** describes a study that aimed to examine the interaction of genetic variation with both distal (self-reported childhood trauma) and proximal momentary stressors on

psychotic experiences in nonclinical and early-psychosis individuals. The present study sought to extend previous literature by investigating the moderating role of highly relevant stress-regulation SNPs on 5 genes (*COMT, RGS4, BDNF, FKBP5, OXTR*) in the association of both kinds of environmental adversity exposures with psychotic experiences and, to examine this moderating genetic effect in nonclinical and early-psychosis participants. It was predicted that the interaction of both distal and proximal environmental factors with the risk alleles/haplotypes of *COMT, RGS4, BDNF, FKBP5 and OXTR* genes would be associated with increased levels of psychotic experiences and that, these associations would be greater in an early psychosis group than in a nonclinical group, given previous reports of increased levels of trauma exposure and stress-sensitivity in persons with psychosis.

The third section of the thesis, ***Genetic moderation of stress sensitization***, further examined the joint contribution of distal and proximal environmental factors in interaction with specific genetic variation relevant to psychosis proneness. Thus, unlike the study described above in *Chapter 2*, the studies comprised in this section analyzed the interplay between both types of environmental exposures and the moderating effect of genetic variation. The general hypothesis was that exposure to early-life adversity heightens the sensitivity to daily-life stressors (stress sensitization) in individuals carrying risk gene variants of some biologically plausible systems relevant for stress sensitivity and makes them more like to react with psychotic experiences in front of these stressors (psychotic reactivity).

The study presented in ***Chapter 3*** examined the interaction of childhood bullying and momentary stressors with *FKBP5* haplotype on the expression of psychotic experiences in nonclinical young adults. This study seeks to expand previous GxE research by examining for the first time the interaction of distal environmental factors and proximal stress re-exposures with

genetic variation linked to HPA reactivity on the expression of psychotic features. It was hypothesized that the interaction between bullying and the *FKBP5* risk haplotype would be associated with higher levels of psychotic experiences and negative affect, but not negative-like features. It was also expected that the association of momentary stress, particularly *social* stress, would be stronger for risk haplotype participants with childhood bullying exposure.

The study described in ***Chapter 4*** further investigated the interplay between self-report childhood trauma, momentary social stress and *COMT* and *OXTR* genetic variability on psychosis proneness. The study sought to provide a novel contribution by examining whether the expression of psychotic experiences is related to the interplay of distal and proximal stress experiences with variation in genes involved in the dopaminergic and oxytocinergic systems. Specifically, it was expected that the impact of childhood trauma in the association of social stress with negative affect and reality distortion experiences would be stronger for Met carriers of the *COMT gene* and for G carriers of the *OXTR* (rs53576). Moreover, it was also expected that individuals with childhood trauma and co-occurrence of Met and G alleles would show increased reactivity to social stress.

The fourth section of the thesis, ***Gene-environment interaction "for worse or better",*** sought to extend our current understanding of the interaction of genes and environment across the extended psychosis phenotype by taking into consideration not only *adversity* but also plausible protective genetic and environmental factors. This goal is embedded in a novel conceptualization of GxE interactions raising the need to contemplate both the 'bad' and 'good' side of genetic sensitivity to the full spectrum of environmental exposures (comprising both negative and positive ones). Thus, ***Chapter 5*** presents the moderating role of *FKPB5* variability in the association of a range of *positive* and *negative* momentary appraisals of contextual (e.g., perception of the situation

as positive or stressful) and interpersonal (e.g., perception of feeling cared for or rejected by others) factors with psychotic experiences in both nonclinical and early-psychosis groups.

Finally, the thesis closes with a general discussion and summary of the key findings, a consideration of the theoretical and intervention implications of such research work, as well as a discussion of the strengths, limitations, challenges and future directions of this research line.

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SECTION 1

THE SYNERGY OF

DISTAL AND PROXIMAL ENVIRONMENTAL FACTORS

ON PSYCHOSIS RISK EXPRESSION

Chapter 1

Impact of Adverse Childhood Experiences on Psychotic-Like Symptoms and Stress Reactivity in Daily Life in Nonclinical Young Adults

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Abstract

Background: There is increasing interest in elucidating the association of different childhood adversities with psychosis-spectrum symptoms as well as the mechanistic processes involved. This study used experience sampling methodology to examine (i) associations of a range of childhood adversities with psychosis symptom domains in daily life; (ii) whether associations of abuse and neglect with symptoms are consistent across self-report and interview methods of trauma assessment; and (iii) the role of different adversities in moderating affective, psychotic-like, and paranoid reactivity to situational and social stressors.

Methods: A total of 206 nonclinical young adults were administered self-report and interview measures to assess childhood abuse, neglect, bullying, losses, and general traumatic events. Participants received personal digital assistants that signaled them randomly eight times daily for one week to complete questionnaires about current experiences, including symptoms, affect, and stress.

Results: Self-reported and interview-based abuse and neglect were associated with psychotic-like and paranoid symptoms, whereas only self-reported neglect was associated with negative-like symptoms. Bullying was associated with psychotic-like symptoms. Losses and general traumatic events were not directly associated with any of the symptom domains. All the childhood adversities were associated with stress reactivity in daily life. Interpersonal adversities (abuse, neglect, bullying, and losses) moderated psychotic-like and/or paranoid reactivity to situational and social stressors, whereas general traumatic events moderated psychotic-like reactivity to situational stress. Also, different interpersonal adversities exacerbated psychotic-like and/or paranoid symptoms in response to distinct social stressors.

Discussion: The present study provides a unique examination of how childhood adversities impact the expression of spectrum symptoms in the real world and lends support to the notion that stress reactivity is a mechanism implicated in the experience of reality distortion in individuals exposed to childhood trauma. Investigating the interplay between childhood experience and current context is relevant for uncovering potential pathways to the extended psychosis phenotype.

Keywords: childhood adversity, psychosis, psychotic-like experiences; stress reactivity; experience sampling methodology

Introduction

There is substantial interest in investigating the etiological relevance of diverse environmental exposures in the development of schizophrenia-spectrum phenotypes [1-3]. Given that mounting evidence supports the hypothesis of etiological continuity between the clinical and subclinical expressions of the schizophrenia spectrum [4-6], focusing on subclinical experiences should enhance the identification of etiological mechanisms while avoiding many of the confounds that complicate the study of clinical samples [7].

Childhood adversity is one environmental exposure that has been widely investigated and shown to be a robust risk factor for schizophrenic phenomenology across a spectrum of severity ranging from schizotypy personality traits to full-blown psychotic disorder [8-10]. In light of this evidence, growing attention is being focused upon elucidating whether particular adverse experiences may contribute to the development of specific symptom domains as well as the mechanistic processes involved [11-13]. These issues are relevant for informing etiological models of symptom formation and may assist the development of prophylactic interventions.

The term childhood adversity has been used in the literature to cover an array of experiences including, among others, different forms of abuse and neglect, bullying victimization, losses, and non-interpersonal events, such as accidents. In general, adverse childhood experiences have been more consistently linked to reality distortion than to negative/disorganized features [10, 14, 15] and available evidence appears to suggest that experiences characterized by an "intention to harm" are more strongly associated with psychotic symptoms than those without intent [16, 17].

It has been proposed that distinct childhood adversities may entail greater risk for different psychosis symptom domains (e.g., [12, 18]). This is based on the hypothesis that different

adversities may exert differential influences upon the unfolding of affective and cognitive processes and may thus be expected to show some degree of symptom specificity [12, 19]. However, empirical findings thus far have provided mixed support to this proposition, with some studies indicating that specific childhood adversities are associated with specific psychotic symptoms (e.g., [19, 20]), and others finding no such evidence of specificity (e.g., [17, 21]).

A shortcoming of several previous studies in the field relates to the assessment of childhood adversity. There is limited research employing comprehensive interview measures and many studies either covered a narrow range of adversities or relied on screening measures of adversity [10, 22]. Furthermore, to our knowledge, it has yet to be examined whether the use of different techniques for assessing adverse experiences (interview versus questionnaire) yields similar associations with psychosis symptom domains. Interview measures of life-stress are generally regarded as superior to questionnaires because they allow for probing and clarification of relevant details and minimize biases related to subjective responding [23-25]. However, interviews are often not feasible in large-scale studies due to the labor and time required for their administration [23, 26, 27]. Utilizing both types of measures within the same study may provide insights about the relevance of the assessment methodology in examining the effects of different adversity exposures.

Another relevant issue that has been scarcely investigated concerns the association of different childhood adversities with symptoms assessed using momentary assessment approaches such as the experience sampling methodology (ESM). ESM is a structured diary technique in which individuals are prompted randomly throughout the day to report on their current experiences, such as emotional states, cognitions, and symptoms. This approach offers several advantages compared to traditional assessment procedures, including enhanced ecological

validity, minimization of retrospective bias, and the possibility of assessing the context of experiences [28-30]. Notably, ESM has been shown to be a useful tool for examining the clinical and subclinical expressions of the schizophrenia spectrum (e.g., [31-35]) and, given that it captures the phenomenology of symptoms as they unfold in the real world, it may complement current efforts to clarify links between adversity subtypes and psychosis symptom domains.

As regards to mechanistic processes, both theoretical and empirical work suggest that one way in which childhood adversity links to positive psychotic phenomena is through a sensitization process that renders individuals more reactive to subsequent minor stressors in everyday life [36, 37]. Indeed, ESM research has shown that childhood adversity is associated with heightened affective reactions to stress in individuals from the general population [38, 39] and with increased affective and psychotic reactions to stress in patients with psychotic disorder [40].

Although these studies have provided valuable insights regarding the impact of childhood adversity on stress reactivity, there remain issues that require further elucidation. For instance, one previous study focused exclusively on experiences of abuse [38] and the others grouped together experiences of abuse and neglect [39, 40]. Therefore, additional research is needed to examine a broader range of childhood adversities and to determine whether specific adversity subtypes moderate affective and/or symptomatic reactivity to stress. Moreover, these studies focused on event-related and activity-related stress. As such, it is unknown whether similar findings may be observed when focusing on other forms of momentary stress, such as social stress. Drawing from stress-sensitization models, it seems plausible and of notable importance that childhood adversities occurring within the context of interpersonal relationships may increase reactivity to daily life stressors falling in the interpersonal realm.

The present study sought to investigate associations between childhood adversity subtypes and psychosis symptom domains as well as the stress sensitization hypothesis in a nonclinical sample of young adults. Specifically, our aims were to (i) examine the association of different childhood adversities (abuse, neglect, bullying by peers, losses, and general traumatic events) with psychotic-like, paranoid, and negative-like symptoms in daily life; (ii) investigate whether associations of abuse and neglect with daily-life symptoms are consistent across different methods of assessment (interview versus self-report); and (iii) examine the role of different adversity subtypes in moderating affective and symptomatic (psychotic and paranoid) reactivity to different forms of momentary stress (i.e., situational and social).

We expected that childhood adversities would be more consistently linked to psychotic-like and paranoid symptoms than to negative-like symptoms, and that experiences of abuse, neglect, and bullying would be associated with greater risk than experiences with a non-intentional nature (losses) and those occurring outside the relational domain (general traumatic events). Furthermore, we expected that both interview and questionnaire measures of abuse and neglect would show associations with daily life symptoms. However, given that comprehensive interviews that rely on objective definitions of adversity allow for a more precise assessment [24, 26] and may be better suited for delineating more specific models of the effects of adversity exposures (e.g., [41]), we hypothesized that more differentiated patterns of association would emerge with interview-based ratings relative to their questionnaire counterparts. Finally, we hypothesized that interpersonal forms of adversity would be relevant in moderating reactivity to both situational and social stress, whereas general traumatic events would be relevant in moderating reactivity to situational stress.

Methods

Ethics Statement

The study was approved by the Ethics Committee of the Universitat Autònoma de Barcelona (Comissió d'Ètica en l'Experimentació Animal i Humana) and conformed to the Helsinki Declaration. The participants had full capacity to consent to participation in research and provided written informed consent prior to taking part in the study.

Participants

The data were collected as part of an ongoing longitudinal investigation examining psychosis risk and resilience in young adults (PSYRIS-Barcelona). Briefly, usable data were obtained from 547 undergraduate students during mass-screening sessions. Of these, a subset of 339 was invited to take part in a comprehensive assessment (comprising laboratory, questionnaire, interview, and ESM measures) with the aim of assessing 200 individuals. Those invited to participate included 189 with standard scores based upon sample norms of at least 1.0 on questionnaire measures of positive or negative schizotypy, and 150 randomly selected participants with standard scores below 1.0. The objective of the enrichment procedure was to ensure adequate representation of schizotypy in the sample. The final sample for this study consisted of 206 participants (78.6% female) from whom usable self-report, interview, and ESM data were collected. The mean age of the sample was 21.3 (SD = 2.4) years.

Materials and Procedure

Clinical psychologists and trained advanced graduate students in clinical psychology administered the measures described below.

Experiences of abuse and neglect. Participants were administered two measures assessing emotional, physical, and sexual abuse and emotional and physical neglect during childhood and adolescence. The first was a self-report measure, the Childhood Trauma Questionnaire (CTQ) [42]. CTQ items are answered on a 5-point Likert-type scale ranging from "never true" to "very often true" and are added to obtain a score for each type of maltreatment. The second measure was the Interview for Traumatic Events in Childhood (ITEC) [24, 43]. The ITEC is a semi-structured interview in which every item endorsed by the participant is followed by questions covering different parameters including the age of onset, perpetrator(s), frequency, duration, and the level of distress associated with the experience (both at the time and in the present). This information is rated according to predefined answer categories and the objective parameters (act, age, perpetrator, frequency, and duration) are used to calculate composite severity scores for each type of maltreatment. In the present study, indices of childhood abuse and neglect were created from the measures described above. Experiences of abuse and neglect are generally characterized as representing maltreatment by commission and omission, respectively [44]. For both the CTQ and ITEC, sum scores of abuse (sum of physical, emotional, and sexual abuse) and neglect (sum of physical and emotional neglect) were used for analyses.

Bullying victimization. Bullying by peers was assessed with questions from the Childhood Experience of Care and Abuse (CECA) [45], a semi-structured, investigator-based interview of childhood experiences. *Bullying is scored on a 4-point scale ranging* from "marked" to "little/none", according to specific rating rules and benchmark examples. The analyses used the continuous severity ratings of bullying victimization.

Losses and general traumatic events. Participants were administered the general trauma subscale from the Early Trauma Inventory (ETI) [46], a semi-structured interview of childhood

trauma. The items in the general trauma subscale cover a wide range of events and do not reflect a unitary construct. Thus, two variables were constructed that assessed: a) experiences of loss and included 5 items: 4 regarding the death of close others (parent or important adult, sibling, friend, and child) and 1 regarding the miscarriage of a child, and b) general traumatic events not occurring in the context of interpersonal relationships and also included 5 items: exposure to a natural disaster, involvement in a serious accident, being the victim of an assault, being the victim of armed robbery, and being held hostage. Scores on these variables were calculated by summing the number of items endorsed, in agreement with previous work (e.g., [47]).

ESM assessments. ESM data were collected on personal digital assistants (PDAs), which signaled participants randomly eight times daily (between 10 a.m. and 10 p.m.) for one week to complete brief questionnaires. When signaled by the PDA, participants had 5 minutes to start the questionnaire. After this time window or the completion of the questionnaire, the PDA became inactive until the next signal. The complete list of ESM items can be found in Barrantes-Vidal et al. [31]. Note that all the ESM items used in the current study were answered on 7-point scales from "not at all" to "very much", with the exception of the social contact item, which was answered dichotomously (alone/with others).

The analyses used ESM measures of symptoms, negative affect, and stress. Following Barrantes-Vidal et al. [31], we created indices of paranoia (2 items: feeling suspicious and mistreated; coefficient $\alpha = 0.70$) and psychotic-like symptoms (8 items: unusual senses, unusual thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and feeling that thoughts/actions are being controlled by someone or something; coefficient $\alpha = 0.74$), and used the item "Right now I have no thoughts or emotions" as a measure of negative-like symptoms. Negative affect was measured

by an index composed of 4 items (feeling anxious, sad, angry, and guilty; coefficient $\alpha = 0.83$). Situational stress was assessed with the item "My current situation is stressful". As for social stress, we distinguished between social stress when participants were alone, assessed by the item "I am alone because people do not want to be with me", and social stress when participants were with others (an index composed of 2 items: not feeling close to others and preferring to be alone; coefficient $\alpha = 0.59$). In addition, the item asking participants whether they were alone or with others at the time of the signal was used to differentiate the effects of social contact from social stress.

Statistical Method

Descriptive statistics and correlational analyses were performed on the childhood adversity variables using the Statistical Package for Social Sciences (SPSS). The statistical analyses involving the ESM data were conducted with Mplus 6 [48]. ESM data have a hierarchical structure in which repeated daily life ratings (level 1 data) are nested within participants (level 2 data). Multilevel or hierarchical linear modeling takes into account the nested structure of the data and is a standard approach for the analyses of ESM data [49].

The multilevel analyses examined two types of relations between the childhood adversity variables and experiences rated in daily life. To examine the association of different types of childhood adversities with daily life symptoms, we computed the independent effects of level 2 predictors (adversity variables) on level 1 dependent measures (ESM ratings). To examine whether childhood adversities moderate the momentary association of stress with experiences in daily life, cross-level interactions were conducted. Cross-level interactions test whether the relations between level 1 predictors (e.g., situational stress) and criteria (e.g., paranoia) vary as a function of level 2 variables (e.g., bullying). Following recommendations of Nezlek [49], level 1 predictors were

group-mean centered and level 2 predictors were grand-mean centered. Note that level 2 predictors can only be grand-mean centered. Level 1 predictors are group-mean centered to minimize the error from between group (person) mean differences. Data departed from normality in some cases, so parameter estimates were calculated using maximum likelihood estimation with robust standard errors. In addition, level 1 criteria exhibiting substantial skew were treated as categorical.

Results

Participants completed an average of 40.8 usable ESM questionnaires (SD = 9.1). Descriptive statistics of the childhood adversity variables and their intercorrelations are displayed in Table 1. Following Cohen [50], correlations of self-reported abuse and neglect with their respective interview counterparts were of a large magnitude. Abuse was associated with neglect both within and across measures, with effect sizes ranging from medium to large. Bullying showed a medium correlation with self-reported and interview-based abuse, and a small correlation with self-reported neglect. Losses and general traumatic events were not associated with any of the other adversity variables.

We examined the independent direct effects of childhood adversity on daily life experiences (Table 2). Both self-reported and interview-based abuse and neglect were associated with increased psychotic-like and paranoid symptoms, whereas only self-reported neglect was associated with having no thoughts or emotions. Bullying was associated with increased psychotic-like symptoms. Interview-based and self-reported abuse and neglect, as well as bullying, were associated with increased negative affect. No associations were found with losses or general traumatic events.

Cross-level interaction analyses examined whether childhood adverse experiences moderated the association of social contact and stress appraisals with psychotic-like symptoms, paranoia, and negative affect in daily life (Tables 3 and 4). As in the analyses of the direct effects, the cross-level effect of each level 2 predictor was examined separately (i.e., level 2 predictors were not entered simultaneously). Each of these analyses computed the association of the level 1 predictor and criterion. Note that the statistical significance of the associations of the level 1 predictor and criterion did not vary across each level 2 predictor, therefore in the table we simply reported the coefficient of the level 1 predictor and criterion for the analysis of CTQ abuse. The results indicated that situational and social stressors were associated with psychotic-like symptoms, paranoia, and negative affect. Being alone at the time of the signal was associated with greater negative affect, but was unrelated to experiencing psychotic-like and paranoid symptoms.

All the childhood adverse experiences were associated with stress-reactivity in daily life. Self-reported abuse moderated the association of social stress when with others with psychotic-like symptoms and that of situational stress with negative affect. Interview-based abuse moderated the association between social stress when with others and paranoia. In addition, both abuse variables moderated the association between situational stress and paranoia and the association between social stress when with others and negative affect. As for experiences of neglect, both self-report and interview ratings moderated the associations of social stress when with others with psychotic-like symptoms, paranoia, and negative affect, along with the association of situational stress with negative affect. Additionally, self-reported neglect moderated the association between situational stress and paranoia, whereas interview-based neglect moderated the association between situational stress and psychotic-like symptoms.

Bullying moderated the slope of social contact and psychotic-like symptoms, such that individuals with higher bullying experienced more psychotic-like symptoms when alone. It also moderated the association of situational stress with paranoia, as well as the associations of social stress when with others with negative affect and paranoia. As seen in Fig 1, when social stress when with others is low, paranoia remains low for everyone; however, as social stress increases, individuals with high levels of bullying experience greater increases in paranoia than those with low levels of bullying.

Experiences of loss moderated the association between feeling unwanted when alone and paranoia. As displayed in Fig 2, this appraisal was associated with increased paranoid symptoms, but only for individuals with high levels of loss. Finally, both losses and general traumatic events moderated the association of situational stress with psychotic-like symptoms, and general traumatic events also moderated the associations of situational stress and social stress when with others with negative affect.

Discussion

The present study used ESM to examine the association of different childhood adverse experiences with psychosis spectrum symptoms as well as the stress reactivity hypothesis in a nonclinically ascertained sample of young adults. The study expanded on previous ESM research by measuring a broader range of childhood adversities (using self-report and interview measures) and by assessing affective and symptomatic reactivity to both situational and interpersonal forms of stress. The findings contribute to our understanding of how childhood adversity subtypes impact the expression of spectrum symptoms in the real world and lend further support to the notion that stress reactivity is a mechanism implicated in the experience of reality distortion in individuals exposed to childhood trauma.

The results regarding the adversity-symptom links were in line with our hypotheses. The finding that abuse, neglect, and bullying were associated with positive symptoms is consistent with recent meta-analyses [9, 51], and, importantly, provides evidence that these relations hold for symptoms experienced in the realm of daily life. The only adversity subtype that was associated with having no thoughts or emotions was self-reported neglect. Prior research has provided mixed support for the association between childhood adversity and negative symptoms [14]. However, our results agree with a recent study that used the CTQ in a sample of patients with psychotic disorder, their siblings, and control participants. They found that abuse was particularly relevant for the positive symptom dimension, whereas neglect showed comparable associations with positive and negative symptoms [52]. Experiences of neglect have been associated with deficits in cognitive, social, and emotional domains [53-55], and may play a role in the development of both positive and deficit-like features. We found that losses and general traumatic events were not associated with any of the symptom domains. This resonates with studies in which experiencing the death of a close person [17], being exposed to a natural disaster [56], and having a serious accident [16] showed either weak or no association with psychosis phenotypes. Collectively, the findings indicate that maltreatment (either by commission or omission) and victimization perpetrated by same-age peers are directly linked to the real-life expression of symptoms.

The current study also aimed to add to the literature by investigating whether associations of abuse and neglect with psychosis symptom domains were consistent across interview and self-report methods of assessment. We found that analogous CTQ and ITEC scores were highly related and showed agreement in their associations with psychotic-like and paranoid symptoms. This is a positive finding for the field given that interview measures are frequently not feasible to employ, especially in large-scale investigations [23]. It is worth noting that the abuse and neglect variables

showed substantial association, which is consistent with numerous studies indicating that abuse and neglect tend to co-occur [57]; however, this does not preclude that each set of experiences could have certain unique effects in shaping psychological states and maladaptive strategies.

As previously noted, the only difference in the direct effects of the childhood adverse experiences on spectrum symptoms was that the negative-like symptom of diminished thoughts/emotions was associated with self-reported (but not interview-based) neglect. Although the reason for this inconsistency is unclear, it may be related to measurement differences between the two instruments. For instance, in addition to the particular features inherent to questionnaire and interview formats, differences in the wording of neglect items (several CTQ neglect, but not abuse, items are reverse-worded [e.g., "My family was a source of strength and support"], whereas none of the ITEC items are) as well as the distinct ways to quantify maltreatment (the CTQ considers frequency whereas the ITEC considers age, perpetrator, frequency, and duration) may account for this discrepancy.

The results regarding stress reactivity replicate and extend previous ESM research [36-38]. We found that all the adverse experiences investigated were associated with increased reactivity to stress in the flow of daily life. It is interesting to note that although losses and general traumatic events were not directly related to positive symptoms, they were associated with increased symptoms only in interaction with momentary stress. This underscores the importance of examining the joint contribution of distal and momentary stressors to risk for psychotic outcomes.

To our knowledge, this is the first study to investigate whether childhood adversities increase reactivity to stress across situational and social domains. Furthermore, by assessing reactions to both social contact and social stress, the study showed that reactivity was not simply

due to being alone or with others, but rather, that it was mostly related to appraisals of social stress. Furthermore, it is worth noting that these findings occurred in a non-clinically ascertained sample of young adults. Thus, childhood adversity may convey risk for subclinical symptoms and stress reactivity in daily life – and these subclinical manifestations may presage the development of schizophrenia-spectrum disorders depending on the complex interaction of genetic, person, and environmental factors across development [58].

Our hypotheses concerning stress reactivity were supported for daily life symptoms. That is, abuse, neglect, bullying, and losses increased psychotic-like and/or paranoid reactivity to situational and social stressors, whereas general traumatic events only increased psychotic-like reactivity to situational stress. Although the findings require replication before drawing firm conclusions, they appear to suggest that only childhood adversities of an interpersonal kind may be relevant for calibrating psychotic-like and paranoid responses to interpersonal stressors. Meanwhile, the findings for negative affect showed a nonspecific pattern of stress-reactivity in relation to the nature of the stressor. Childhood trauma may sensitize individuals to react with increased negative affect, regardless of the specific nature of the distal adversity or the proximal daily life stressor, given the fundamental role of negative affect in the experience of adversity and subsequent re-exposures.

Different interpersonal adversities were found to exacerbate psychotic-like and/or paranoid symptoms in response to distinct social stressors. Specifically, abuse, neglect, and bullying were associated with increased reactivity to social stress when with others, whereas losses were associated with increased reactivity to social stress when alone. In recent years, research findings have converged in supporting a role for negative models/schemas of the self and others in the pathway between interpersonal adversities and psychotic phenomena (e.g., [59-61]). According to

attachment theory, early relational experiences shape internal working models (cognitive/affective representations) of the self and others that guide how individuals construe their transactions with the social world [62, 63]. Importantly, internal working models may be activated by appraisals of internal or external threat—and this appraisal process and ensuing regulatory efforts may vary according to an individual's relational history [63, 64]. Drawing from these notions and prior research, our results may suggest that experiencing social stress *when with others* may be salient for activating negative models in individuals who have experienced neglectful/hostile behavior *from others*. On the other hand, feeling unwanted *when alone* may be salient for activating negative models among those who have experienced loss. The activation of these negative models by specific interpersonal stressors may trigger cognitive and perceptual anomalies leading to the experience of reality distortion.

The strengths of the present work include the comprehensive assessment of childhood adverse experiences, which was conducted using fine-grained interview measures and an extensively used questionnaire, as well as the use of ecologically valid measures of symptoms and stress obtained in real time and on multiple occasions during the course of one week. Limitations of the study include its cross-sectional nature, which precludes conclusions about the causal effects of childhood adversities. Likewise, causal inferences concerning the effects of daily life stressors cannot be definitively drawn, given that predictor and criterion ESM measures were assessed concurrently. In addition, our use of a predominantly female university student sample limits the generalizability of the findings to community samples and clinical populations. At the same time, however, employing a nonclinical sample allows for the assessment of mechanistic processes without the confounding effect of the consequences of a psychotic disorder and minimizes concerns about unreliability of childhood adversity reports due to clinical status. Another

consideration is that only one item (having no thoughts or emotions) specifically examined negative symptoms, which may have limited our ability to detect associations between trauma exposures and other negative-like phenomenology. Two issues are noteworthy regarding our assessment of negative symptoms. First, various items in our ESM questionnaire tapped aspects of negative symptoms (e.g., I like what I am doing –reversed- captures anhedonia), but only one (no thoughts or emotions) assessed a markedly deviant experience. These other items tapping negative-like symptoms were designed following recommendations on the assessment of negative symptoms with ESM suggesting that these should be measured in terms of (diminished) experiences of affect, cognition, interest, and social functioning in real life [35]. Naturally, other experiences may contribute to the responses given to these items. In this study, we restricted our comparison to those questions measuring a clear deviant experience, which is the case for all positive symptoms and for the one negative symptom. Secondly, it must be noted that there is a limit to the number of questions that can be included in an ESM protocol, given the frequent and repeated assessments performed during the day. As most evidence has found a more consistent or strong association of adversity exposures with positive rather negative psychotic experiences (e.g., [10, 15]), our questionnaire focused on the latter.

In closing, this study further refines our understanding of how adversity-symptom associations are expressed in real life and the way in which childhood adversity subtypes influence stress reactivity dynamics that may lie on the pathway to the positive dimension of the extended psychosis phenotype. The findings can help inform developmental models of psychosis vulnerability and may have implications for identifying key targets for prophylactic intervention among individuals exposed to childhood adversity.

Table 1. Descriptive Statistics of Adverse Childhood Experiences and their Intercorrelations (n=206)

	M	***SD***	**Range**	**Abuse CTQ**	**Neglect CTQ**	**Abuse ITEC**	**Neglect ITEC**	**Bullying**	**Loss**	**Traumatic Events**
Abuse CTQ	17.89	4.85	15-48	-	***0.52***	***0.54***	**0.45***	**0.33***	0.03	0.00
Neglect CTQ	15.26	4.38	10-32		-	**0.43***	***0.50***	0.21**	0.05	-0.00
Abuse ITEC	5.03	6.16	0-48			-	**0.45***	**0.42***	0.05	0.11
Neglect ITEC	3.11	5.45	0-30				-	0.09	0.05	0.05
Bullying	0.62	0.93	0-3					-	0.02	0.01
Loss	0.66	0.62	0-3						-	0.11
Traumatic Events	0.32	0.54	0-2							-

Note: CTQ = Childhood Trauma Questionnaire; ITEC = Interview for Traumatic Events in Childhood.

*p<0.05, **p<0.01, ***p<0.001. Medium effect sizes (r≥0.30) in bold, large effect sizes (r≥0.50) in bold and italics.

Table 2. Independent Direct Effects of Adverse Childhood Experiences on Daily Life Outcomes (n=206)

Level 1 Criterion	**Level 2 Predictors**						
	Abuse CTQ	**Neglect CTQ**	**Abuse ITEC**	**Neglect ITEC**	**Bullying**	**Loss**	**Traumatic Events**
	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)	γ_{01} (*df* = 204)
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Psychosis Spectrum							
Psychotic-like index	0.009 (0.003)**	0.009 (0.003)**	0.007 (0.002)**	0.006 (0.003)*	0.034 (0.015)*	0.028 (0.019)	0.034 (0.023)
Paranoia index	0.022 (0.008)**	0.023 (0.007)**	0.016 (0.004)***	0.013 (0.006)*	0.038 (0.026)	0.044 (0.038)	0.044 (0.044)
No thoughts/emotions†	-0.002 (0.027)	0.102 (0.039)*	0.007 (0.022)	0.009 (0.034)	0.289 (0.168)	0.177 (0.274)	0.329 (0.280)
Affect							
Negative affect index	0.035 (0.008)***	0.027 (0.008)**	0.024 (0.006)***	0.018 (0.008)*	0.113 (0.040)**	0.058 (0.056)	0.078 (0.067)

Note: CTQ = Childhood Trauma Questionnaire; ITEC = Interview for Traumatic Events in Childhood.

†Items were run as categorical. *p<0.05, **p<0.01, ***p<0.001

Table 3. Cross-Level Interactions of Adverse Childhood Experiences with Daily Life Experiences (n=206)

Level 1 Criterion	**Level 1 Predictors**		**Level 2 Predictors**			
			Abuse CTQ	**Neglect CTQ**	**Abuse ITEC**	**Neglect ITEC**
		γ_{10} (*df* = 204)	γ_{11} (*df* = 204)	γ_{11} (*df* = 204)	γ_{11} (*df* = 204)	γ_{11} (*df* = 204)
		Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Psychotic-like index	Situation stressful	0.035 (0.004)***	0.001 (0.001)	0.001 (0.001)	0.001 (0.001)	0.002 (0.001)*
Psychotic-like index	Alone	0.000 (0.006)	-0.001 (0.001)	0.001 (0.001)	-0.001 (0.002)	-0.001 (0.001)
Psychotic-like index	Alone b/c not wanted	0.082 (0.019)***	0.001 (0.003)	0.007 (0.005)	-0.002 (0.002)	0.000 (0.003)
Psychotic-like index	Social stress index	0.019 (0.004)***	0.002 (0.001)*	0.003 (0.001)**	0.001 (0.001)	0.002 (0.001)*
Paranoia index	Situation stressful	0.078 (0.010)***	0.005 (0.002)*	0.006 (0.002)*	0.003 (0.001)*	0.004 (0.002)
Paranoia index	Alone	-0.008 (0.014)	-0.001 (0.003)	-0.002 (0.003)	0.001 (0.002)	-0.001 (0.003)
Paranoia index	Alone b/c not wanted	0.153 (0.050)**	-0.002 (0.009)	0.001 (0.012)	-0.006 (0.006)	0.000 (0.008)
Paranoia index	Social stress index	0.060 (0.011)***	0.005 (0.003)	0.007 (0.003)*	0.007 (0.002)***	0.006 (0.003)*
Negative affect index	Situation stressful	0.214 (0.012)***	0.005 (0.002)**	0.005 (0.002)*	0.002 (0.001)	0.005 (0.002)*
Negative affect index	Alone	-0.047 (0.018)*	-0.002 (0.004)	-0.003 (0.005)	0.000 (0.003)	-0.001 (0.004)
Negative affect index	Alone b/c not wanted	0.176 (0.050)***	-0.002 (0.009)	0.001 (0.014)	-0.002 (0.005)	-0.008 (0.010)
Negative affect index	Social stress index	0.109 (0.013)***	0.006 (0.002)**	0.007 (0.003)*	0.004 (0.002)*	0.007 (0.003)*

Note: CTQ = Childhood Trauma Questionnaire; ITEC = Interview for Traumatic Events in Childhood.

*p<0.05, **p<0.01, ***p<0.001

Table 4. Cross-Level Interactions of Adverse Childhood Experiences with Daily Life Experiences (n=206)

Level 1 Criterion	**Level 1 Predictors**		**Level 2 Predictors**		
			Bullying	**Loss**	**Traumatic Events**
		γ_{10} (*df* = 204)	γ_{11} (*df* = 204)	γ_{11} (*df* = 204)	γ_{11} (*df* = 204)
		Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Psychotic-like index	Situation stressful	0.035 (0.004)***	0.006 (0.006)	0.015 (0.007)*	0.024 (0.009)**
Psychotic-like index	Alone	0.000 (0.006)	-0.015 (0.006)*	-0.012 (0.011)	0.009 (0.013)
Psychotic-like index	Alone b/c not wanted	0.082 (0.019)***	0.019 (0.023)	0.011 (0.037)	-0.013 (0.037)
Psychotic-like index	Social stress index	0.019 (0.004)***	0.005 (0.004)	0.008 (0.006)	0.017 (0.009)
Paranoia index	Situation stressful	0.078 (0.010)***	0.029 (0.012)*	0.018 (0.018)	0.035 (0.019)
Paranoia index	Alone	-0.008 (0.014)	0.001 (0.014)	0.004 (0.022)	0.043 (0.029)
Paranoia index	Alone b/c not wanted	0.153 (0.050)**	0.039 (0.053)	0.190 (0.078)*	0.017 (0.119)
Paranoia index	Social stress index	0.060 (0.011)***	0.029 (0.013)*	0.037 (0.019)	0.020 (0.023)
Negative affect index	Situation stressful	0.214 (0.012)***	0.015 (0.012)	0.005 (0.022)	0.061 (0.020)**
Negative affect index	Alone	-0.047 (0.018)*	0.012 (0.018)	-0.047 (0.027)	0.015 (0.032)
Negative affect index	Alone b/c not wanted	0.176 (0.050)***	0.075 (0.044)	0.119 (0.084)	0.098 (0.114)
Negative affect index	Social stress index	0.109 (0.013)***	0.032 (0.015)*	0.025 (0.019)	0.053 (0.024)*

*p<0.05, **p<0.01, ***p<0.001

Fig 1. Cross-level interaction of the association of bullying with the slope of social stress when with others and paranoia.

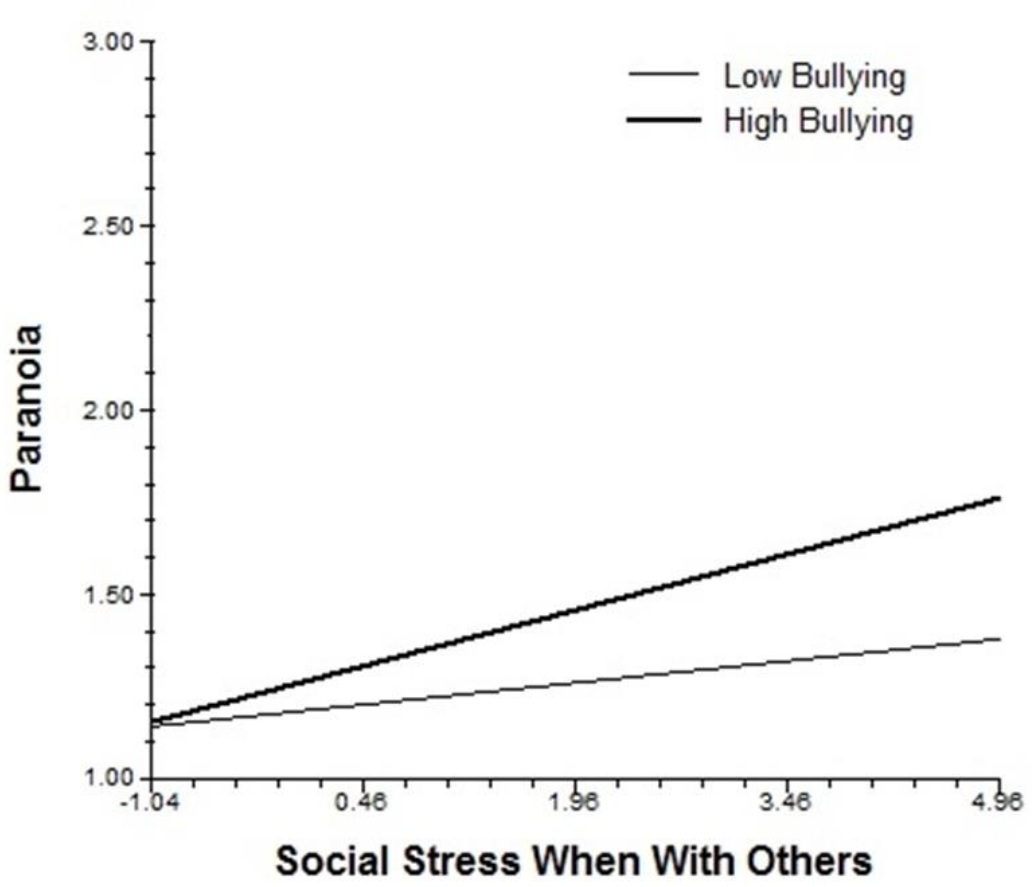
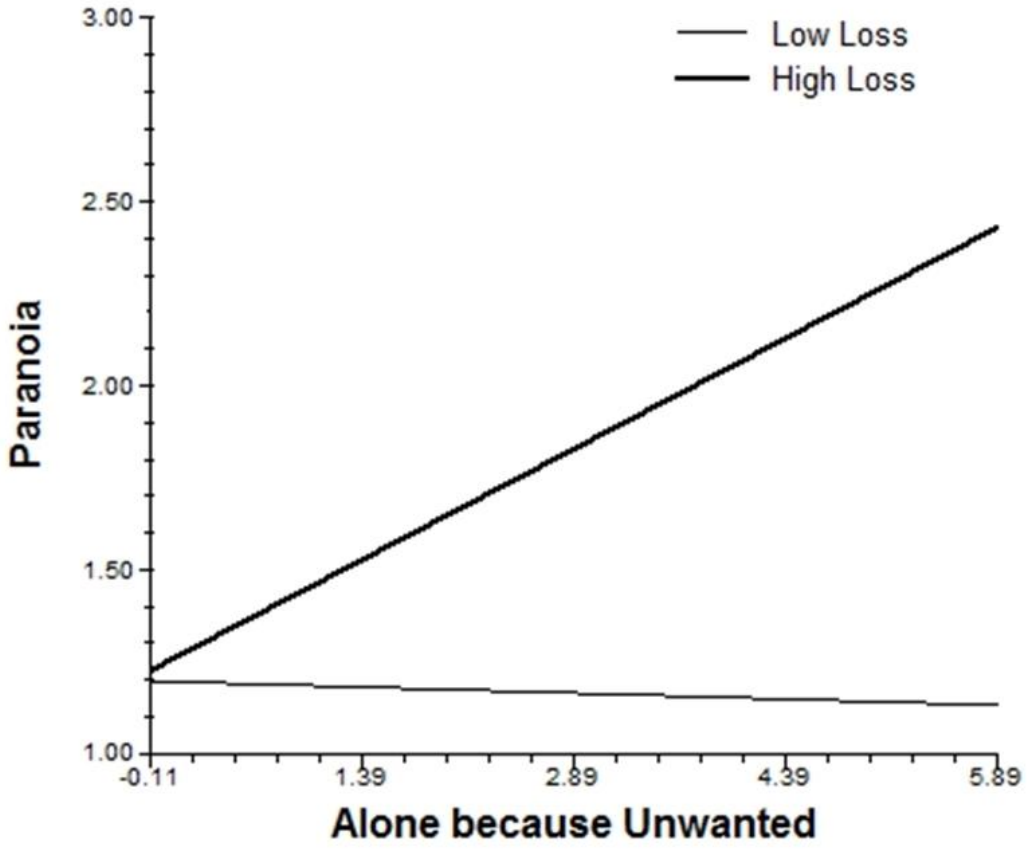


Fig 2. Cross-level interaction of the association of loss with the slope of feeling unwanted by others when alone and paranoia.



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SECTION 2

IMPACT OF GENE-ENVIRONMENT INTERACTION

ON THE REAL-LIFE EXPRESSION OF

PSYCHOTIC EXPERIENCES

Chapter 2

Do stress-regulation genes moderate the real world association of stress and psychotic experiences in early psychosis?

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Abstract

Background: Psychotic experiences (PEs) involve a complex interplay of genetic and environmental factors. However, the interaction of both distal and proximal environmental factors with genetic variation for stress-regulation biological systems across the extended psychosis phenotype is understudied. The present study used experience sampling methodology to investigate the (i) interaction of relevant stress-related SNPs on *COMT, RGS4, BDNF, FKBP5* and *OXTR* genes with both distal (early-life) and proximal (current, momentary) stress on PEs in an extended psychosis sample; and (ii) differences between early-psychosis and nonclinical groups for these interactions.

Method: A total of 242 nonclinical young adults and 96 early-psychosis participants were prompted randomly eight times daily for one week to complete assessments of their current experiences (e.g., PEs), and stress appraisals. Participants were also administered a self-report measure to assess childhood trauma and were genotyped for 10 SNPs on *COMT, RGS4, BDNF, FKBP5* and *OXTR* genes.

Results: Unlike genetic variants, both distal and proximal psychosocial stressors were associated with PEs in the nonclinical and early-psychosis samples. In both cases, they were more strongly associated with PEs in the early-psychosis than in the nonclinical group. The interactions of the risk haplotype of *RGS4* and *FKBP5* with distal, but not proximal, stressors were associated with momentary levels of PEs. No interactions emerged with *COMT or BDNF* variants. The interaction of the A risk allele of *OXTR* (rs2254298) with momentary proximal (situational) stress was associated with PEs only in the early-psychosis group.

Discussion: This study extends previous research by showing that individual differences in relevant stress-regulation systems interact with *both* distal (childhood trauma) and proximal (momentary real-life) psychosocial stressors in shaping the real-world manifestation of psychotic phenomena across nonclinical and clinical levels of the hypothetical continuum of psychosis.

Keywords: Early psychosis, at-risk mental states, schizotypy, psychotic-experiences, stress-sensitivity, gene-environment interaction, ecological validity

Introduction

Converging evidence suggests that the psychosis phenotype is expressed across a dynamic continuum that ranges from subclinical (e.g, schizotypy, psychotic-like experiences), nonpsychotic (e.g., schizotypal personality disorder) to full-blown psychotic manifestations (Kwapil & Barrantes-Vidal, 2015; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). In recent years, increasing focus has been placed on studying persons at the early stages of psychosis, such as those with at-risk mental states for psychosis (ARMS) and first episode psychosis (FEP). These populations allow us to examine potentially etiologically relevant mechanisms of psychotic disorders without the marked confounding factors seen in chronic patients (McGorry et al., 2010). Notably, several studies report an overlap of etiological factors, as well as phenomenological and developmental processes, across high schizotypy, clinical risk, and clinical populations (e.g., Barrantes-Vidal, Grant, & Kwapil, 2015; Reininghaus et al., 2016a).

Distal and proximal psychosocial stress exposure has been identified as an important risk factor for psychosis. Both childhood adversity and momentary stressors in the flow of daily life have been associated with psychotic features across the extended psychosis phenotype (e.g., Barrantes-Vidal et al., 2013; Reininghaus et al., 2016a; Varese et al., 2012; Velikonja, Fisher, Mason, & Johnson, 2015). At the same time, and consistent with the hypothesized etiopathogenic relevance of these psychosocial factors, psychosis populations have higher levels of trauma exposure and stress-sensitivity (e.g., Holtzman, Shapiro, Trotman, & Walker, 2012).

Gene-environment interaction research (GxE) highlights the synergistic effect between environmental and genetic risk factors across subclinical and clinical expressions of the psychotic phenotype (e.g., Barrantes-Vidal et al., 2015; Uher et al., 2014). In this sense, a limited but

increasing number of GxE studies have shown that certain single nucleotide polymorphisms (SNPs) interact with distal and proximal stress to heighten risk for psychotic experiences (PEs; e.g., Holtzman et al., 2013). Importantly, some of these studies have employed ambulatory assessment strategies (e.g., experience sampling method [ESM] or ecological momentary assessment [EMA]) to examine the interplay of gene and environment in the realm of daily life (e.g., van Winkel et al., 2008a). Such studies offer the advantage of minimizing retrospective bias and enhancing ecological validity (Csikszentmihalyi & Larson, 1992).

A number of SNPs have been most prominently investigated as moderators of adverse environmental exposures given their functional impact on individual differences for biologically relevant systems in stress-regulation. One such example is the functional polymorphism Val66Met on the brain-derived neurotrophic factor (*BDNF*) gene, which involves a change from Valine (Val) to Methionine (Met) at code 66 (located on chromosome 11p14). The Val allele has been associated with increased release of BDNF protein, which is critically involved in neuronal development, differentiation and plasticity processes (Notaras & van den Buuse, 2015). Individuals with the risk Met allele of the *BDNF* gene reported more feelings of paranoia in response to momentary social stress than those with the Val-Val genotype (Simons et al., 2009). Similarly, Met carriers reported more PEs when they were exposed to childhood abuse compared to Val-Val individuals (Alemany et al., 2011; de Castro-Catala et al., 2016).

One of the most studied neurobiological mechanisms underlying the association of distal and momentary stress with PEs has been the dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis (van Winkel et al., 2008b). Hence, genetic variation involved in the regulation of stress response system (e.g., the FK506 binding protein 5 (*FKBP5*) gene located on chromosome 6p21) has also received particular attention. Specifically, the minor "high-induction" alleles (C, A, T, T)

of at least 4 *FKBP5* SNPs (rs3800373, rs9296158, rs1360870, and rs9470080, respectively) have been associated with an abnormal prolongation of the stress response (Binder, 2009). Previous research has indicated that *FKBP5* variability interacted with distal stress in the expression of PEs in clinical and nonclinical samples (Ajnakina et al., 2014; Alemany et al., 2016; Collip et al., 2013; Cristóbal-Narváez et al., 2016). However, there is no evidence of the interaction between momentary stress and *FKBP5* variability on PE across the extended psychosis phenotype.

Accumulating evidence suggests that dysregulation of the HPA axis may precipitate a cascade of events leading to dopamine dysregulation in key brain areas (e.g., prefrontal cortex; PFC) implicated in the emergence of psychotic symptoms (Kapur et al., 2003; van Winkel, Stefanis, & Myin-Germeys, 2008b). In light of these findings, genetic variation in dopamine-related genes (e.g., the catechol-O-methyltransferase (*COMT*) located on chromosome 22q11.2) has been extensively studied in the context of stress-reactivity in psychosis. In particular, the functional polymorphism *COMT*Val158Met involves an amino acid change from Val to Met, which affects the activity of COMT enzyme involved in the inactivation of catecholamines at postsynaptic sites in the brain, chiefly in the PFC (Lotta et al., 2005). The Met-Met genotype has been associated with decreased COMT activity and, subsequently, with higher dopamine levels in the PFC in comparison to Val-Val genotype (Chen, Wang, O'Neill, Walsh, D., & Kendler 2004).

Previous studies have found differential effects of *COMT* Val158Met in clinical and nonclinical samples (e.g., de Castro-Catala et al. 2015). Whereas three ESM studies found that individuals homozygous for the Met risk allele showed more psychotic and/or affective reactivity to stress than Val carriers in clinical samples (van Winkel et al., 2008a; Collip et al., 2011, Peerbooms et al., 2012), one ESM study found that Val-Val individuals reported more paranoid reactivity than Met carriers in a general population sample (Simons et al., 2009). Similarly,

whereas one study revealed that the severity of PEs was greater for Met-Met individuals with exposure to childhood adversities in a clinical sample (Green et al., 2014), another found that Val-Val individuals who have experienced distal stress were more likely to endorse PEs in a nonclinical sample at a trend level (Ramsay et al., 2013).

An alternative candidate gene that also impacts dopamine signaling and prefrontal function is the regulator of G-protein signaling 4 (*RGS4*) gene located on chromosome 1q23 (Buckholtz et al., 2007). RGS4 is a GTPase-activator that participates in the hydrolysis of GTP back to GDP, shortening adequately the duration of signal transduction of several neurotransmitters (e.g., dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA). Two prior studies have found an association of risk alleles of two *RGS4* polymorphisms (rs951436, rs2661319) with the subclinical manifestations of the psychosis phenotype (Stefanis et al., 2008; de Castro-Catala et al., 2016). Nevertheless, the role of *RGS4* variability in the context of stress reactivity in psychosis has not yet been studied.

Another promising candidate for understanding individual differences in the response of the dopaminergic and stress response systems is the neuropeptide oxytocin (Sauer, Montag, Reuter, & Kirsch, 2013). Recent studies have revealed that the neuropeptide oxytocin and its receptor (*OTXR*) modulate a variety of human social functions, including the propensity to use social interactions for damping HPA reactivity effects (Feldman, Monakhov, Pratt, & Ebstein 2016). In light of these findings, two *OXTR* SNPs (rs53576, rs2254298) that comprise a guanine (G) to adenine (A) substitution on the *OXTR* gene (located on chromosome 3p25) have been identified as relevant in the context of mental disorders associated with social deficits (Kumsta & Heinrichs, 2013). Crucially, the interconnections between the dopamine and oxytocin systems has led to the suggestion that individuals with more efficient variants (i.e., the G alleles of both *OXTR*

SNPs) may more adaptively regulate the salience assigned to social stimuli (Shamay-Tsoory & Abu-Akel, 2016), thus diminishing susceptibility to psychopathology. Nonetheless, it is unknown whether distal and momentary stress interact with *OXTR* variability in the expression of PEs.

Overall, to the best of our knowledge, there are no GxE studies examining the interaction of genetic variants with both distal and proximal stress on PEs in daily life across the extended psychosis phenotype. The present study sought to complement the extant literature by investigating the moderating role of these stress-regulation relevant SNPs (*COMT*, *RGS4*, *BDNF*, *FKBP5*, and *OXTR*) on environmental stress exposures across the extended psychosis phenotype. The first aim was to concurrently examine the interaction of both distal (childhood trauma) and proximal (momentary) stress with genetic variation on PEs. The second aim was to examine whether the interaction of childhood trauma or real-life assessments of momentary stress (situational and social stress) with genetic variation on PEs differed between early-psychosis and nonclinical groups. We predicted that the interaction of both distal and proximal environmental factors with the risk alleles/haplotypes of *COMT*, *RGS4*, *BDNF*, *FKBP5* and *OXTR* genes would be associated with increased PEs and that these associations would be greater in an early-psychosis sample than in a nonclinical sample, given previous reports of increased levels of trauma exposure and stress-sensitivity in persons with psychosis.

Methods

Ethics Statement

The study was approved by the Ethics Committee of the Universitat Autònoma de Barcelona (Comissió d'Ètica en l'Experimentació Animal i Humana) and conformed to the

Helsinki Declaration. The participants had full capacity to consent to participation in research and provided written informed consent prior to taking part in the study.

Participants

The data were collected as part of an ongoing longitudinal investigation examining psychosis risk and resilience (PSYRIS-Barcelona). The nonclinical sample was drawn from an original unselected sample of 808 young adults, which included 547 undergraduate students from the Universitat Autònoma de Barcelona and 261 students from technical training schools in Barcelona. A detailed description of the sampling procedures can be found in Barrantes-Vidal et al. (2013) and only a brief overview is provided here. A subset of these participants was invited to take part in an in-depth assessment including self-report, interview, laboratory and ESM measures. We invited participants who had standard scores based upon sample norms of at least 1.0 on the positive or negative schizotypy dimensions of the Wisconsin Schizotypy Scales (WSS; Chapman, Chapman, & Raulin, 1976; Chapman, Chapman, & Raulin, 1978; Eckblad & Chapman, 1983; Eckblad, Chapman, Chapman, & Mishlove, 1982), the suspiciousness scale of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), or the positive symptom subscale of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002), and randomly selected participants who had standard scores below 1.0 on each of these. The goal of the enrichment procedure was to ensure adequate variability of schizotypy traits and avoid having a "super healthy" control sample. The final nonclinical sample comprised 242 participants.

The early-psychosis sample was recruited in the Sant Pere Claver-Early Psychosis Program (SPC-EPP; Domínguez-Martínez et al., 2011). A total of 96 early-psychosis participants (60 ARMS and 36 FEP) were included in the present study. Patients' inclusion criteria were age

between 14 and 40 years old, IQ ≥ 75, and a proper command of Spanish language. ARMS-criteria were established by the Comprehensive Assessment of At-Risk Mental States (CAARMS) and/or the Schizophrenia Proneness Instrument-Adult version (SPI-A). FEP-patients met DSM-IV-TR criteria for any psychotic disorder or affective disorder with psychotic symptoms as established by the Structured Clinical Interview for DSM-IV (SCID-I). Descriptive characteristics of the whole sample are displayed in Table 1.

Materials and Procedure

Distal stress variables. Participants were administered the Childhood Trauma Questionnaire (CTQ), a self-report measure that assesses emotional, physical, and sexual abuse and emotional and physical neglect during childhood and adolescence. CTQ items are answered on a 5-point Likert-type scale ranging from "never true" to "very often true" and are added to obtain a score for each type of maltreatment. In the present study, the total CTQ score (i.e., the sum of the 5 subscale scores) was used for analyses.

ESM proximal stress and PEs variables. ESM data were collected on personal digital assistants (PDAs) that signaled participants randomly eight times daily (between 10 a.m. and 10 p.m.) for one week to complete brief questionnaires. When signaled by the PDA, participants had 5 minutes to start the questionnaire. After this time window or the completion of the questionnaire, the PDA became inactive until the next signal. All ESM items reported in the current study were answered on 7-point scales from "not at all" to "very much".

The analyses used ESM items assessing PEs and appraisals of proximal or momentary stress (situational and social; details can be found in Barrantes-Vidal et al. 2013). We created an index of PEs using the following 10 items: feeling suspicious, mistreated, unusual senses, unusual

thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and passivity (coefficient $\alpha = 0.87$ in the nonclinical sample, coefficient $\alpha = 0.95$ in the early-psychosis sample). The appraisal of situational stress was assessed with the item "My current situation is stressful". Social stress appraisals during social contact were assessed by two items: "I feel close to this person (people)" (reversed) and "Right now I would prefer to be alone".

Genetic data. All subjects were asked to provide a biological sample consisting of buccal mucosa on cotton swabs or blood. Genomic DNA was extracted using the Realpure genomic DNA extraction kit and the Realpure DNA "sss" extraction kit (Durviz S.L.U., Valencia, Spain) for the buccal mucosa and blood samples, respectively. Ten SNPs within the *COMT*, *BDNF*, *OXTR*, *FKBP5*, and *RGS4* genes were genotyped using TaqMan 5' exonuclease assay (Applied Biosystems). Details on the SNPs are given in Table 2. The final volume of the polymerase chain reaction (PCR) was of 5µL, containing 5ng of genomic DNA, 2.5µL of TaqMan Master Mix, and 0.125µL of 40x genotyping assay for all SNPs, except for the *COMT* rs4680 which contained 0.25 µL of 20x genotyping assay (see assay codes in Table 2). The cycling parameters were 95ºC for 10 minutes followed by 40 cycles of denaturation at 92ºC for 15 seconds and annealing/extension at 60ºC for 1 minute. PCR plates were read on an ABI PRISM 7900HT instrument with SDS v2.1 software (Applied Biosystems). For accuracy of genotyping, twenty percent of samples, chosen randomly, were genotyped twice. Compliance with Hardy-Weinberg Equilibrium was assessed for each SNP (all $p < 0.05$).

Linkage disequilibrium (LD) between SNPs within the same gene was examined by pair-wise comparisons of r^2 and D' using Haploview version 4.2 (Barrett et al., 2005). High LD was observed between the four *FKBP5* SNPs and between the two *RGS4* SNPs (both with $r^2 > 0.7$ and

D' > 0.9), but not between the *OXTR* SNPs ($r^2 < 0.04$ D' < 0.6). Estimation of *FKBP5* and *RGS4* haplotype combination per subject was conducted using a Bayesian approach implemented with PHASE software (Stephens & Donnelly, 2003). To better examine our hypothesis, participants were divided into the following groups based on previous studies (Cristobal-Narvaez et al., 2016; de Castro-Catala et al., 2016; Stefanis et al., 2008; Zannas & Binder et al., 2014): 1) carriers of at least one risk haplotype, 2) carriers of one risk haplotype and one protective haplotype, and 3) carriers of at least one protective haplotype. Thus the haplotype groups for the *FKBP5* haplotype were 1) AGCC/-, 2) AGCC/CATT and 3) CATT/- ; for the *RGS4* haplotype 1) TA/-, 2) TA/GG and 3) GG/-. Haplotypic frequencies are presented in Table 2.

Statistical Method

Descriptive statistics were performed on the childhood trauma and ESM variables using the Statistical Package for Social Sciences (SPSS) Version 19.0 (IBM Corp, 2010). ESM data have a hierarchical structure in which repeated daily life ratings (level 1 data) are nested within participants (level 2 data). Linear mixed models were used to control for within-subject clustering of multiple observations using the "xtmixed" command in Stata 12 (StataCorp, 2011). Graphs were generated with the R program (www.r-project.org). Analyses were performed on the total pool of participants, that is, on a total sample comprising nonclinical and early-psychosis participants, treating group as a variable when necessary.

The multilevel analyses examined two types of relations between genetic and environmental variables across the extendend psychosis phenotype. First, in order to examine whether the interactions between environmental (distal and proximal) and genetic (4 SNPs and 2 haplotypes) variables on PEs were significant in the total sample, the main effects of environmental and genetic variables (e.g., distal stress and *FKBP5* haplotype) were entered simultaneously at the

first step, and the interaction term (e.g., distal stress x *FKBP5* haplotype) was entered at the second step to examine its contribution over and above the main effects.

Second, we examined whether the interactions between environmental (distal and proximal) and genetic (4 SNPs and 2 haplotypes) variables on PEs differ between nonclinical and early-psychosis groups. Therefore, the three main effects were entered at the first step (e.g., distal stress, *FKBP5* haplotype and group variables), the three two-way interaction terms (e.g., distal stress x group, *FKBP5* haplotype x group, distal stress x *FKBP5* haplotype) were entered at the second step, and the three-way interaction term was entered at the third step (e.g., distal stress x *FKBP5* haplotype x group). When a significant interaction was found, the effect of the interaction was examined using simple slopes analyses. Distal and proximal stress were used as continuous variables for analyses. Genotypes were coded 0, 1, 2 using an additive genetic model. However, when genotype comparison was required, we also used a dummy variable coding. Six multilevel linear regressions, one for each genetic variation investigated, were conducted to test each hypothesis; therefore the *p-value* based on the Bonferroni correction was $p = 0.05/6 = 0.0083$.

Results

GxE interactions in the total sample

As shown in Table 3, distal stress and both situational and social proximal appraisals were associated with PEs in daily life in the total sample, whereas no main effects of genetic variation on PEs were found. The two-way interactions between genetic and environmental variables on PEs indicated that only the interaction of distal stress with the *FKBP5* ($p = 0.007$) and *RGS4* risk haplotypes ($p = 0.008$) were associated with increased PEs. As expected, simple slopes analyses indicated that distal stress was associated with greater increases in PEs for individuals carrying the

FKBP5 risk haplotype (CATT/- :0.028, *SE* = 0.008, *p* = 0.000; AGCC/CATT: 0.022, *SE* = 0.005, *p* = 0.000; AGCC/-:0.010, *SE* = 0.003, *p* = 0.000). Additionally, dummy-coded variables were created for genotype comparison purposes. As shown in Figure S1, participants carrying the *FKBP5* risk haplotype (CATT/- and AGCC/CATT) showed greater increases in PEs compared to non-risk individuals (CATT/- vs AGCC/-: 0.018, *SE* = 0.007, *p* = 0.011; AGCC/CATT vs AGCC/-: 0.012, *SE* = 0.006, *p* = 0.035; CATT/- vs AGCC/CATT: 0.006, *SE* = 0.007, ns). Similarly, simple slopes analyses indicated that distal stress was associated with greater increases in PEs for individuals carrying the *RGS4* risk haplotype (TA/- :0.029, *SE* = 0.005, *p* = 0.000; TA/GG: 0.017, *SE* = 0.002, *p* = 0.000; GG/-:0.015, *SE* = 0.004, *p* = 0.000). As shown in Figure S2, participants carrying the risk haplotype (TA/-) experienced more PEs than TA/GG carriers (TA/- vs TA/GG: 0.020, *SE* = 0.006, *p* = 0.000) and, at a trend level, more so than non-risk individuals (TA/- vs GG/-: 0.014, *SE* = 0.007, *p* = 0.057). No differences were found between TA/GG and GG/- haplotype groups (TA/GG vs GG: -0.006, *SE* = 0.007, ns).

Group differences in the interaction between distal and proximal environmental and genetic variables

As shown in Tables 4-5, the group variable was also associated with PEs, indicating that early-psychosis participants reported more PEs in daily life than nonclinical participants. The two-way interactions between environmental and group variables showed that, in most models (except for the *COMT* and *RGS4*) environmental variables (both distal and proximal) were more strongly associated with PEs in the early-psychosis group. None of the two-way interactions of genetic variation with group were associated with PEs.

The three-way interaction of distal stress, *FKBP5* haplotype and group was significantly associated with PEs, such that childhood trauma was associated with increased PEs for participants

with the *FKBP5* risk haplotype in the early-psychosis group. Simple slope analyses indicated that the *FKBP5* risk haplotype moderated the association between distal stress and PEs in the early-psychosis, but not in the nonclinical group (early-psychosis: 0.024, *SE* = 0.09, *p* = 0.007; nonclinical: -0.004, *SE* = 0.002, ns). In addition, analyses of the *FKBP5* haplotype in the early-psychosis group showed that distal stress was associated with increased PEs for CATT/- and AGCC/CATT participants (CATT/-: 0.057, *SE* = 0.019 p = 0.002; AGCC/CATT: 0.029, *SE* = 0.014 p = 0.044), but not for those carrying the AGCC/- haplotype (AGCC/: 0.003, *SE* = 0.006, ns; see Figure 1).

Similarly, the three-way interaction among distal stress, *RGS4* haplotype and the group variable was significantly associated with PEs. This indicated that distal stress was associated with increased PEs for participants with the *RGS4* risk haplotype in the early-psychosis compared to the nonclinical group. Simple slopes analyses indicated a consistent trend for the early-psychosis group although it did not reach statistical significance (early-psychosis: 0.017, *SE* = 0.010, ns; nonclinical: -0.003, *SE* = 0.003, ns). Additionally, analyses of the *RGS4* haplotype in the early-psychosis group showed that distal stress was associated with increased PEs for the risk haplotype TA/- participants (0.034, *SE* = 0.009 *p* = 0.000), but not for those carrying the GG/- or TA/GG haplotype (GG/-: 0.750, *SE* = 0.929, *p* = 0.42; TA/GG: 1.170, *SE* = 0.161, *p* = 0.055; see Figure 2).

The three-way interactions also examined whether the interaction of proximal stress (both situational and social appraisals) with genetic variation on PEs differed between nonclinical and early-psychosis groups. As shown in Table 4, only the three-way interaction of situational stress, *OXTR* rs2254298 and group was significantly associated with PEs. This interaction indicated that situational stress was associated with increased PEs for participants with the A allele in the early-

psychosis group. Simple slope analyses indicated that the A allele of the *OXTR* gene moderated the association between situational stress and PEs in the early-psychosis group but not in the nonclinical group (early-psychosis: 0.048, *SE* = 0.022, *p* = 0.031; nonclinical: -0.001, *SE* = 0.008, ns). In addition, analyses of the *OXTR* in the early psychosis group showed that situational stress was associated with greater increases in PEs for AA and AG participants (AA: 0.255, *SE* = 0.063 *p* = 0.000; GA: 0.138, *SE* = 0.028 *p* = 0.000) as compared with those carrying the GG genotype (GG: 0.089, *SE* = 0.014, *p* = 0.000; see Figure 3). As expected, dummy coding indicated that A-allele carriers (AA and AG) experienced more PEs than GG subjects (AA vs GG: 0.135, *SE* = 0.037, *p* = 0.000; GA vs GG: 0.057, *SE* = 0.015, *p* = 0.000; AA vs GA: 0.078, *SE* = 0.038, *p* = 0.038).

Finally, although some three-way interactions also seemed to appear in *COMT* (rs4680), *OXTR* (rs53576) and, *BDNF* (rs6265) models, these results did not reach significance after controlling for multiple testing.

Discussion

The present study extended previous GxE studies in psychosis by examining with ecological validity the interplay of genetic variants with both distal and proximal psychosocial environmental factors on the real-life expression of PEs. Both distal and momentary (situational and social) stress were associated with increased levels of PEs in the flow of daily life, whereas none of the genetic variants studied was directly associated with PEs. GxE interactions of the risk haplotype of *RGS4* and *FKBP5* with distal, but not proximal, stress were associated with the expression of PEs in the total sample. Moreover, when both groups were compared, results indicated that both factors were more strongly associated with PEs in the early-psychosis group as

compared to the nonclinical group. In the early-psychosis group, the interactions of distal stress with the risk haplotype of *RGS4* and *FKBP5* were associated with increased levels of PEs, whereas the interaction of momentary situational stress with the risk allele of *OXTR (*rs2254298) was associated with PEs in the realm of daily life.

The association of both distal and proximal environmental factors with PEs is consistent with a growing body of research showing that psychosocial stress - such as childhood trauma and daily-life situational and social stress - is associated with schizotypy traits and subclinical and clinical expressions of the psychosis phenotype (Barrantes-Vidal et al., 2013; Myin-Germeys, van Os, J., Schwartz, Stone, & Delespaul, 2000; Reininghaus et al., 2016a). As expected, and consistent with previous studies, individuals of the early-psychosis group reported greater levels of PEs as well as childhood trauma and stress appraisals (e.g., Holtzman el al., 2012), and the association of both stressors with PEs was also greater in this early-psychosis group compared to the nonclinical group (even if the latter was oversampled for elevated scores on schizotypy and PEs to include a wide range of variability in terms of psychosis-proneness).

Converging research has shown that individuals with a higher psychosis liability display an exacerbated response to daily life stressors as a result of a sensitization process caused by previous exposures to early and severe stress (e.g., Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011; Reininghaus et al., 2016b). Our results are consistent with the sensitization hypothesis, as distal stress exposures seemed to result in a lasting liability in the form of psychotic reactivity (even though please note that we did not test out directly the interaction of early-life with momentary stress in this particular study). On the other hand, in line with previous studies (e.g., Trotman et al., 2014), help-seeking individuals presented greater daily life psychotic reactivity to both types of stressors compared with nonclinical, which suggests that, although

comparable mechanisms, such as stress-sensitivity, operate across different levels of psychotic liability and expression, there are also differences. Results thus seem to indicate the existence of both shared risk factors and mechanisms in the two groups as well as a differential impact of stress that possibly relates to both levels of exposure and to resilience factors critical for clinical expression.

Our analysis of the moderating role of stress-regulation SNPs on environmental stress exposures showed that the interactions of the risk haplotypes of *RGS4* and *FKBP5* genes with distal, but not proximal, stress were associated with PEs in the total sample. Importantly, the group comparison indicated that such GxE findings only held for the early-psychosis group and, again, only for distal stress. This resonates with recent studies (Klengel & Binder, 2015) showing that, unlike momentary stress, the exposure of early-life stress may lead to long-lasting molecular mechanisms in relevant stress-response systems, shaping individual differential trajectories and resulting in a greater risk for the development of psychopathological outcomes. In this line, prior studies have consistently demonstrated that exposure to childhood trauma increases the risk for several stress-related phenotypes for carriers of the minor alleles (C, A, T, T) of *FKBP5* SNPs (rs3800373, rs9296158, rs1360870, and rs9470080; e.g., Binder et al., 2009) or for the risk haplotype including these 3 or 4 alleles (e.g., Binder et al., 2004; Klengel et al., 2013). Specifically, these risk alleles have been associated with decreased sensitivity of the glucocorticoid receptor (GR) to circulating cortisol, entailing a diminished negative feedback regulation of the HPA axis and hence, enduring responses to stress (Binder, 2009). Notably, a relevant finding consistent with the discrepancy of both stressors with *FKBP5* variability is that specifically early-life stress (but not current cortisol levels or adult trauma exposure) in interaction with *FKBP5* risk alleles induce epigenetic changes that result in individual differences in GR sensitivity, ultimately leading to the

dysregulation of the stress response and an increased vulnerability for psychopathological phenotypes (Klengel et al., 2012). These authors suggested that there may exist a crucial development stage for such epigenetic changes altering the homeostasis of HPA axis and causing subsequent abnormal responses to stress. This is also consistent with compelling evidence suggesting that the dysregulation of HPA axis may play a critical role in the expression of the positive dimension of psychotic phenomena (Kapur et al., 2003; Read, van Os, Morrison, & Ross, 2005) due to the synergistic relation between glucocorticoid secretion and an elevated dopaminergic activity in specific brain regions (e.g., mesolimbic regions; van Winkel et al., 2008).

Similarly, the *RGS4* risk haplotype moderated the association between distal, but not proximal stress and PEs. Although, to the best of our knowledge, this is the first GxE study showing evidence of the interplay between psychosocial stress and *RGS4* genetic variation on PEs, neurobiological research has indicated that the *RGS4* gene, because of its function and biological properties, may be a relevant candidate gene for psychotic outcomes (e.g., de Castro-Catala et al., 2016). It has been shown that it is highly expressed in important brain regions involved in the pathophysiology of schizophrenia (e.g., PFC) and, importantly, it also shows an increased responsiveness to environmental stimuli, being able of modulating the function of G-protein coupled neurotransmitter receptors critically implicated in schizophrenia-related disorders (Chowdari et al., 2008; Levitt, Ebert, Mirnics, Nimgaonkar & Lewis, 2006). In this line, evidence from animal studies has indicated a complex regulation of RGS4 expression subsequent to chronic forms of stress. It was shown that specific regions of the rat brain implicated in stress responsiveness (e.g., paraventricular nucleus, locus coeruleus), displayed a differential regulation of *RGS4* expression that may also contribute to the dysregulation of the glucocorticoid-induced negative feedback and the prolongation of stress responses (Ni et al., 1999). In this context, our

significant results of distal stress with *FKBP5* and *RGS4* risk haplotypes, suggest that after childhood trauma exposure, both variants may be involved in the HPA axis dysregulation associated with the risk for PEs across the extended psychosis phenotype.

Conversely, the interaction of *OXTR* (rs2254298) risk allele with momentary stress was associated with PEs in the early-psychosis group. Notably, a rapidly growing body of evidence from human and animal studies has indicated that oxytocin may diminish behavioral and physiological responses to stress. For instance, it has been shown in humans that oxytocin administration has stress-buffering effects decreasing subjective stress experiences (Kumsta & Heinrichs, 2003), and also diminishes amygdala activation in response to stressors (e.g., Domes et al., 2007; Petrovic, Kalisch, Singer, & Dolan, 2008). Notably, the two SNPs on *OXTR* (rs2254298, rs53576) have been associated with individual differences in intermediate mechanisms (e.g., affiliation, stress-regulation, empathy) underlying the risk for psychopathological phenotypes – especially those with social dysfunction features (e.g., Feldman, Monakhov, Pratt, & Ebstein, 2016). Although there is no prior evidence showing that, in particular, allelic variation (rs2254298) may moderate the association of stress with psychotic outcomes, several studies have linked this genetic variation (rs2254298) with increased risk for psychopathological outcomes (e.g., Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2011) and with important brain areas involved in stress reactivity and emotional responses, such as the hypothalamus and amygdala (e.g., Tost et al. 2011). Interestingly, one study revealed that A carriers of rs225498 showed higher PANSS general symptom scores than GG individuals in a group of persons with schizophrenia, whereas no differences were found within a healthy control group (Montag et al., 2013). In light of these findings, it is attractive to speculate that early-psychosis individuals carrying at least one A allele of rs225498 may present a maladaptive regulation to negative environmental factors in the realm

of daily life (e.g., stressful situations), increasing the susceptibility to psychopathology. In this sense, this allelic variation has been specifically associated with individual differences in attachment styles (e.g., Feldman et al., 2016), and the interplay between *OXTR* genetic variation and attachment styles may be a mechanism involved in maladaptive stress regulation leading to a greater risk for psychopathology. Further research should elucidate whether the interaction of attachment measures and individual differences in *OXTR* gene may play a role in stress reactivity and its relation to psychopathological outcomes.

Our results provide new insights on how the interplay of genetic variation within *FKBP5*, *RGS4* and *OXTR* genes with distal or proximal environmental factors impacts the expression of PEs in early-psychosis compared to the nonclinical group. In addition, some interactions of environmental factors with *BDNF* and *COMT* variability also seemed to be associated with PEs; however, they did not reach statistical significance after controlling for multiple testing. Further studies with more statistical power or using an estimation of *BDNF* and *COMT* haplotypes, which allows a higher detection of GxE interactions, are needed in order to elucidate the plausible interplay of both distal and proximal stress with these genetic variants.

The strengths of this study include the comparison of a nonclinical and early-psychosis sample, the use of ecologically valid measures of symptoms and stress in real life during multiple time points over a week, and the estimation of two risk haplotypes increasing the power to detect genetic associations (Crawford et al., 2005), thus increasing the power and reliability of GxE research (Myin-Germeys et al., 2009). Limitations of the study include its cross-sectional nature, which limits interpretations about the causal effects of GxE interactions. Similarly, causal inferences examining the effects of stress cannot be definitively drawn, given that predictor and criterion ESM variables were measured concurrently. It should also be noted that although the nonclinical

sample was oversampled for schizotypy to ensure adequate variance in psychosis liability, it does not constitute a homogenously high schizotypy sample. That is, the sample is composed of both high, medium and low schizotypy scorers, and the high scores refer to both the positive and negative schizotypy dimensions (which may involve different etiological mechanisms). Therefore, the sample composition precludes us from drawing precise conclusions of the role of schizotypy in the gxe interactions examined in the present study. Future research may focus on the examination of these GxE interactions in high and low schizotypy groups, analyzing the positive and negative dimensions independently.

Table 1. Demographic characteristics and ESM and genetic variables across the extended psychosis phenotype

Sample	**Early-Psychosis (n=96)**		**Nonclinical (n=242)**		
	M	**N**	***M***	**N**	**Statistic test**
Sex (M/F%)	69/31	96	26/74	242	X^2= 53.15, df = 1, p < 0.001
Age, years (Mean±SD)	22.26 (4.64)	96	20.03 (2.88)	242	t = 5.34; df =336, p < 0.001
Childhood Trauma (Mean±SD)	41.38 (12.91)	84	33.46 (8.24)	242	t = 6.48; df =324, p < 0.001
ESM variables					
Psychotic-like Symptoms (Mean±SD)	1.58 (0.79)	96	1.15 (0.22)	242	t = 7.74; df =336; p < 0.001
Situation Stressful (Mean±SD)	2.28 (1.22)	96	2.14 (1.05)	242	t = 1.10; df =336; ns
Social Closeness (Mean±SD)	5.22 (1.30)	95	5.55 (0.87)	242	t = -2.69; df =335; p < 0.01
Prefer to be Alone (Mean±SD)	2.33 (1.32)	95	1.73 (0.76)	242	t = 5.22; df =335; p < 0.001

Table 2. Details on the genetic polymorphisms included in the present study

Gene	SNP or haplotype	Alleles (major/minor)	MAF	AB assay code	Genotypic or haplotypic frequencies (n (%))		
					Genotype or haplotype	Early-psychosis sample	Nonclinical sample
COMT	rs4680	G/A (Val/Met)	0.37	C_25746809_50	Val/Val Val/Met Met/Met	29 (35%) 40 (48%) 14 (17%)	80 (33%) 115 (48%) 47 (19%)
BDNF	rs6265	G/A (Val/Met)	0.20	C_11592758_10	Val/Val Val/Met Met/Met	61 (71%) 22 (26%) 3 (3%)	159 (66%) 72 (30%) 11 (4%)
OXTR	rs2254298	G/A	0.21	C_15981334_10	GG GA AA	58 (66%) 25 (29%) 4 (5%)	169 (70%) 63 (26%) 10 (4%)
	rs53576	G/A	0.39	C_3290335_10	GG GA AA	32 (38%) 41 (48%) 12 (14%)	104 (44%) 105 (45%) 25 (11%)
FKBP5	rs3800373	A/C	0.33	C_27489960_10	AA AC CC	8 (9%) 40 (46%) 39 (45%)	25 (10%) 104 (43%) 113 (47%)
	rs9296158	G/A	0.36	C_1256775_10	GG GA AA	36 (41%) 40 (46%) 11 (13%)	109 (45%) 108 (45%) 25 (10%)
	rs1360780	C/T	0.33	C_8852038_10	CC CT TT	38 (44%) 40 (46%) 9 (10%)	115 (47%) 101 (42%) 26 (11%)
	rs9470080	C/T	0.36	C_92160_10	CC CT TT	36 (41%) 38 (44%) 13 (15%)	106 (44%) 107 (44%) 29 (12%)
	Haplotype	-	-	-	CATT/- AGCC/CATT AGCC/-	12 (14%) 33 (38%) 41 (48%)	32 (14%) 85 (36%) 116 (50%)
RGS4	rs951436	T/G	0.37	C_9619634_10	TT TG GG	30 (35%) 36 (42%) 20 (23%)	75 (31%) 107 (45%) 57 (24%)
	rs2661319	A/G	0.37	C_16265745_10	AA AG GG	26 (30%) 40 (47%) 20 (23%)	68 (28%) 104 (44%) 67 (28%)
	Haplotype	-	-	-	TA/- TA/GG GG/-	30 (35%) 36 (41%) 21 (24%)	73 (31%) 98 (41%) 67 (28%)

AB, Applied Biosystems; EUR, European reference population from 1000 genomes project; MAF, Global minor allele frequency according to 1000 genomes.

Table 3. Two-way Interactions between Environmental Stress Variables and Genetic Variables on Psychotic Experiences

Psychosocial Stress	***COMT*** **rs4680**	***BDNF*** **rs6265**	***OXTR*** **rs2254298**	***OXTR*** **rs53576**	***FKBP5*** **haplotype**	***RGS4*** **haplotype**
Distal variable	n = 316	n = 318	n = 319	n = 309	n = 309	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Childhood trauma	0.016 (0.002)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***
Genetic variation (G)	0.008 (0.034)	0.057 (0.043)	0.020 (0.044)	-0.031 (0.037)	0.010 (0.035)	0.029 (0.032)
Childhood trauma x G	0.005 (0.004)	-0.008 (0.005)	-0.003 (0.005)	-0.004 (0.004)	0.009 (0.003)*	0.009 (0.004)*
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 325
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Situational stress	0.054 (0.049)***	0.053 (0.005)***	0.055 (0.005)***	0.053 (0.005)***	0.056 (0.005)***	0.055 (0.005)***
Genetic variation (G)	0.006 (0.024)	0.023 (0.034)	-0.005 (0.034)	-0.051 (0.029)	0.023 (0.027)	0.029 (0.025)
Situational stress x G	0.001 (0.007)	0.001 (0.008)	0.015 (0.009)	0.002 (0.007)	0.007 (0.007)	-0.001 (0.006)
Social closeness	-0.023 (0.004)***	-0.019 (0.004)***	-0.023 (0.004)***	-0.019 (0.004)***	-0.023 (0.005)***	-0.023 (0.004)***
Genetic variation (G)	-0.003 (0.030)	0.013 (0.043)	0.015 (0.043)	0.033 (0.037)	0.038 (0.035)	0.027 (0.032)
Social closeness x G	0.002 (0.006)	0.000 (0.006)	-0.003 (0.008)	-0.004 (0.005)	-0.000 (0.006)	-0.005 (0.006)
Prefer to be alone	0.034 (0.006)***	0.032 (0.005)***	0.035 (0.006)***	0.034 (0.005)***	0.036 (0.006)***	0.036 (0.006)***
Genetic variation (G)	-0.023 (0.023)	0.058 (0.033)	0.005 (0.033)	0.032 (0.029)	0.009 (0.027)	0.024 (0.025)
Prefer to be alone x G	0.007 (0.008)	-0.017 (0.009)	0.002 (0.010)	0.003 (0.008)	0.006 (0.008)	0.008 (0.008)

+$p \leq 0.05$ *$p \leq 0.01$, **$p \leq 0.005$, ***$p \leq 0.001$. Note. In order to examine the two-way interaction between genetic and environmental variables, we first assessed the two main effects of E and G in the same model and then entered the interaction term over and above the two main effects.

Table 4. Three-way Interactions of Group Status (Early-psychosis versus Nonclinical), Proximal and Distal Environmental Stress Variables and Genetic Variables on Psychotic Experiences

Psychosocial Stress	***COMT*** **rs4680**	***BDNF*** **rs6265**	***OXTR*** **rs2254298**	***OXTR*** **rs53576**	***FKBP5*** **haplotype**	***RGS4*** **haplotype**
Distal variable	n = 316	n = 318	n = 319	n = 309	n = 309	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Childhood trauma	0.012 (0.002)***	0.013 (0.002)***	0.013 (0.002)***	0.014 (0.003)***	0.013 (0.003)***	0.013 (0.003)***
Genetic variation (G)	0.014 (0.032)	0.055 (0.040)	0.012 (0.041)	-0.018 (0.035)	0.008 (0.033)	0.024 (0.030)
Group	0.343 (0.055)***	0.345 (0.056)***	0.360 (0.057)***	0.350 (0.057)***	0.365 (0.058)***	0.358 (0.057)***
Childhood trauma x Group	0.011 (0.005)+	0.015 (0.005)**	0.014 (0.005)**	0.015 (0.005)**	0.014 (0.005)**	0.011 (0.005)+
G x Group	-0.006 (0.080)	0.242 (0.098)+	0.021 (0.095)	-0.075 (0.083)	0.021 (0.079)	0.121 (0.074)
Childhood Trauma x G	0.002 (0.004)	-0.010 (0.005)+	-0.002 (0.004)	0.002 (0.004)	0.008 (0.003)+	0.005 (0.004)
Childhood Trauma x G x Group	-0.001 (0.009)	-0.020 (0.010)+	-0.009 (0.009)	0.003 (0.008)	0.030 (0.006)***	0.023 (0.007)**
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Situational stress	0.054 (0.005)***	0.053 (0.004)***	0.055 (0.005)***	0.054 (0.005)***	0.056 (0.005)***	0.056 (0.005)***
Genetic variation (G)	0.010 (0.023)	0.033 (0.032)	-0.006 (0.032)	-0.038 (0.028)	0.023 (0.026)	0.022 (0.024)
Group	0.202 (0.038)***	0.250 (0.041)***	0.247 (0.041)***	0.245 (0.042)***	0.248 (0.042)***	0.245 (0.041)***
Situational stress x Group	0.075 (0.011)***	0.068 (0.010)***	0.073 (0.010)***	0.069 (0.010)***	0.074 (0.011)***	0.073 (0.010)***
G x Group	0.018 (0.054)	0.097 (0.076)	-0.039 (0.072)	-0.122 (0.062)+	0.116 (0.058)+	0.110 (0.054)+
Situational stress x G	0.003 (0.007)	0.003 (0.008)	0.013 (0.008)	0.006 (0.007)	0.007 (0.007)	-0.002 (0.006)
Situational stress x G x Group	0.008 (0.015)	0.019 (0.018)	0.051 (0.018)**	0.004 (0.015)	0.018 (0.015)	0.012 (0.014)

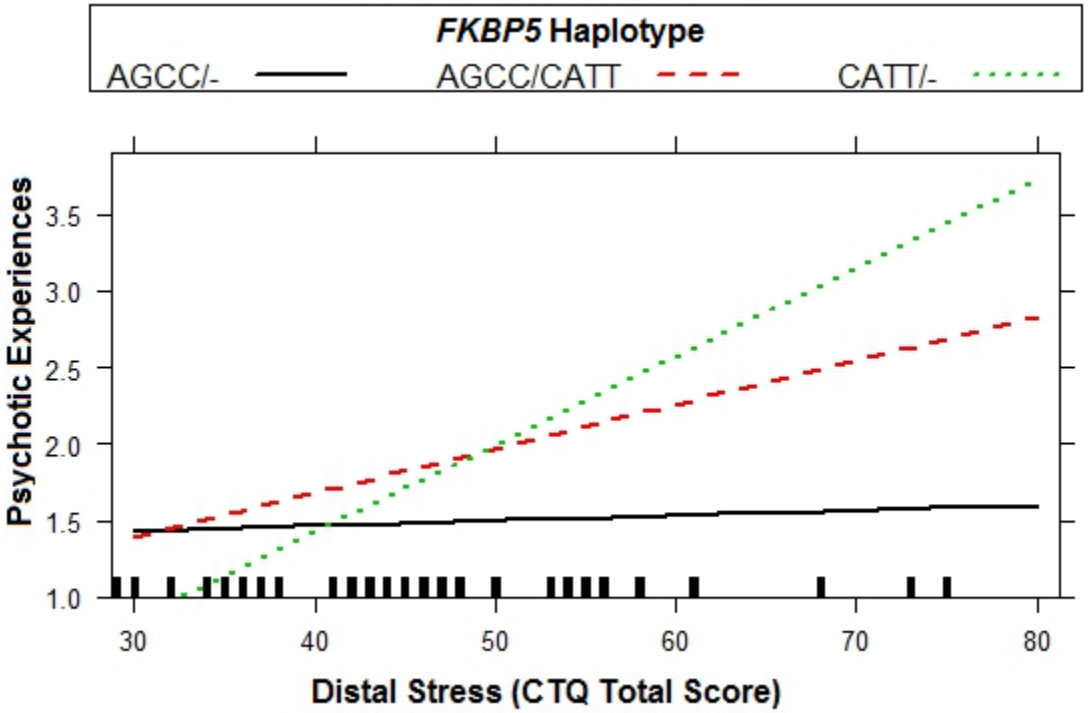
+p≤0.05 *p≤0.01, **p≤0.005, ***p≤0.001

Table 5. Three-way Interactions of Group Status (Early-psychosis versus Nonclinical), Distal Environmental Social Stress Variables and Genetic Variables on Psychotic Experiences.

Psychosocial Stress	***COMT*** **rs4680**	***BDNF*** **rs6265**	***OXTR*** **rs2254298**	***OXTR*** **rs53576**	***FKBP5*** **haplotype**	***RGS4*** **haplotype**
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Social closeness	-0.023 (0.004)***	-0.019 (0.003)***	-0.022 (0.004)***	-0.019 (0.004)***	-0.022 (0.005)***	-0.022 (0.004)***
Genetic variation (G)	0.005 (0.029)	0.028 (0.041)	0.011 (0.041)	0.018 (0.035)	0.035 (0.033)	0.023 (0.030)
Group	0.272 (0.048)***	0.353 (0.053)***	0.349 (0.052)***	0.353 (0.054)***	0.351 (0.053)***	0.349 (0.052)***
Social closeness x Group	-0.049 (0.010)***	-0.033 (0.008)***	-0.043 (0.010)***	-0.033 (0.008)***	-0.045 (0.010)***	-0.043 (0.010)***
G x Group	0.018 (0.070)	0.080 (0.098)	-0.004 (0.092)	0.105 (0.079)	0.166 (0.074)+	0.121 (0.069)+
Social closeness x G	0.005 (0.006)	-0.001 (0.006)	-0.003 (0.008)	-0.002 (0.005)	0.001 (0.006)	-0.004 (0.006)
Social closeness x G x Group	0.032 (0.015)+	-0.015 (0.016)	0.003 (0.019)	-0.025 (0.012)+	0.004 (0.014)	0.001 (0.013)
Prefer to be alone	0.035 (0.006)***	0.033 (0.004)***	0.035 (0.006)***	0.034 (0.005)***	0.036 (0.006)***	0.036 (0.006)***
Genetic variation (G)	-0.014 (0.022)	0.065 (0.032)+	0.001 (0.032)	0.020 (0.028)	0.007 (0.026)	-0.001 (0.023)
Group	0.215 (0.037)***	0.267 (0.041)***	0.262 (0.041)***	0.266 (0.042)***	0.262 (0.042)***	0.263 (0.041)***
Prefer to be alone x Group	0.051 (0.013)***	0.040 (0.011)***	0.051 (0.012)***	0.040 (0.011)***	0.052 (0.013)***	0.050 (0.013)***
G x Group	0.005 (0.053)	0.105 (0.076)	-0.052 (0.071)	0.109 (0.062)	0.086 (0.058)	0.021 (0.054)
Prefer to be alone x G	0.008 (0.008)	-0.016 (0.009)	0.002 (0.010)	0.001 (0.008)	0.005 (0.008)	0.007 (0.007)
Prefer to be alone x G x Group	-0.024 (0.018)	0.013 (0.020)	0.021 (0.021)	0.009 (0.016)	0.008 (0.018)	0.029 (0.016)

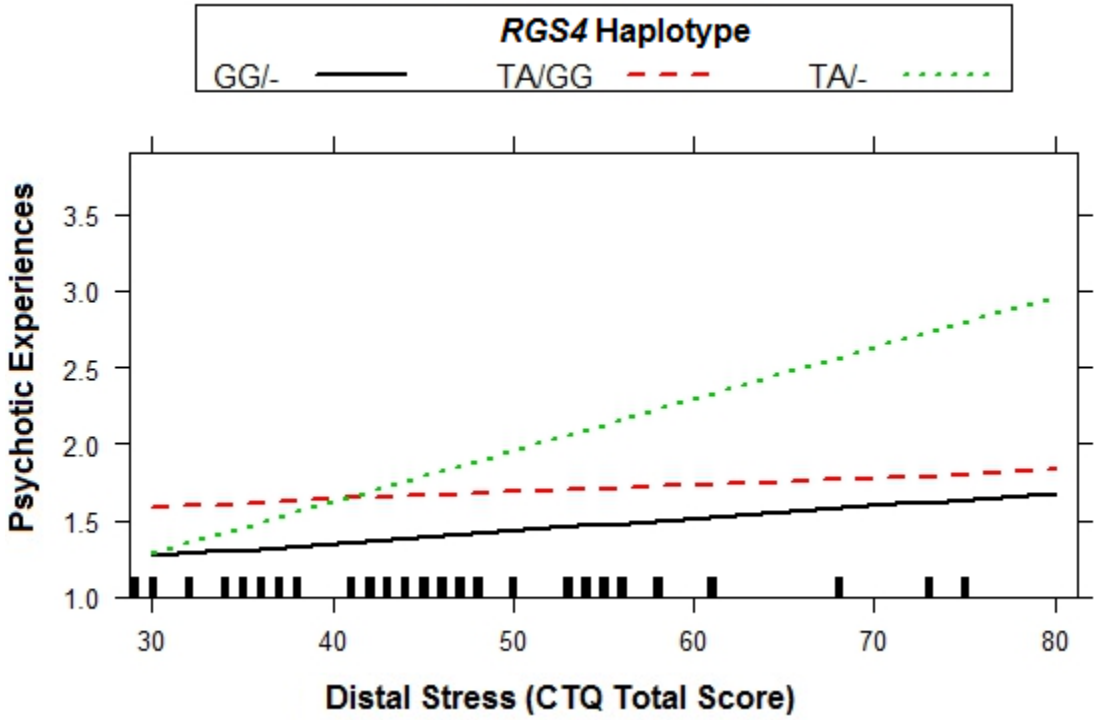
+p≤0.05 *p≤0.01, **p≤0.005, ***p≤0.001

Fig 1. Interaction between Distal Stress and *FKBP5* haplotype on Psychotic Experiences in Early-psychosis Individuals



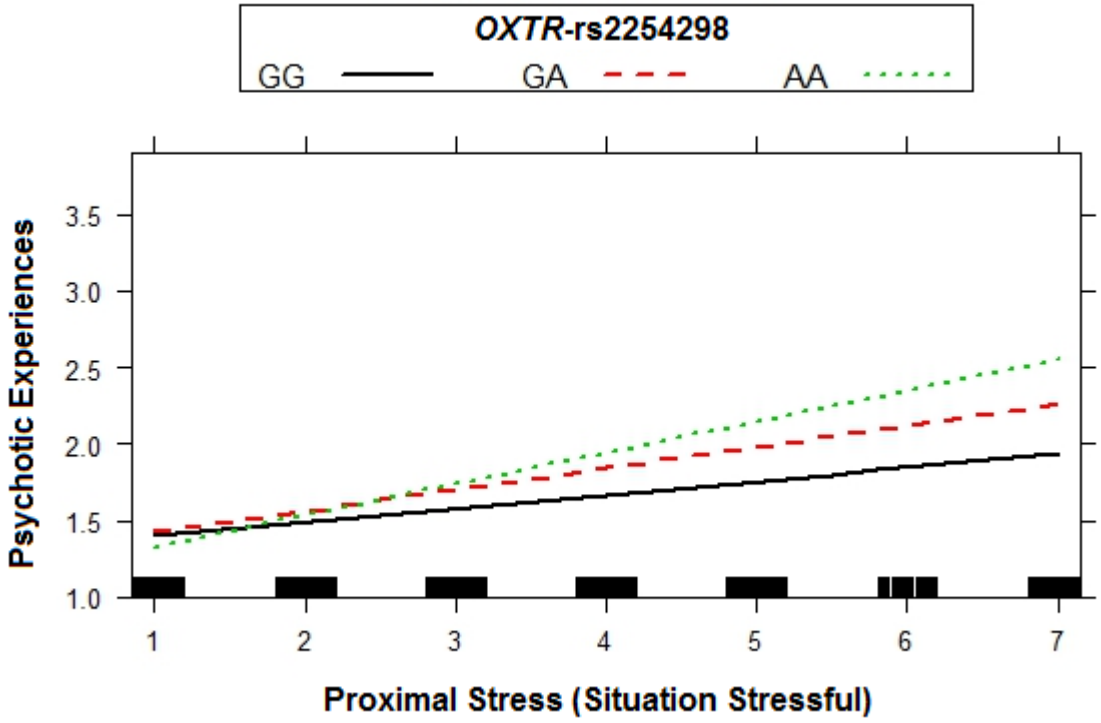
Note that the groups for the *FKBP5* haplotype were: 1) carriers of at least one risk haplotype (CATT/-), 2) carriers of one risk haplotype and one protective haplotype (AGCC/CATT), and 3) carriers of at least one protective haptlotype (CATT/-.).

Fig 2. Interaction between Distal Stress and *RGS4* haplotype on Psychotic Experiences in Early-psychosis Individuals



Note that the groups for the *RGS4* haplotype were: 1) carriers of at least one risk haplotype (TA/-), 2) carriers of one risk haplotype and one protective haplotype (TA/GG), and 3) carriers of at least one protective haptlotype (GG/-.).

Fig 3. Interaction between Proximal Stress and *OXTR*-rs2254298 on Psychotic Experiences in Early-psychosis Individuals



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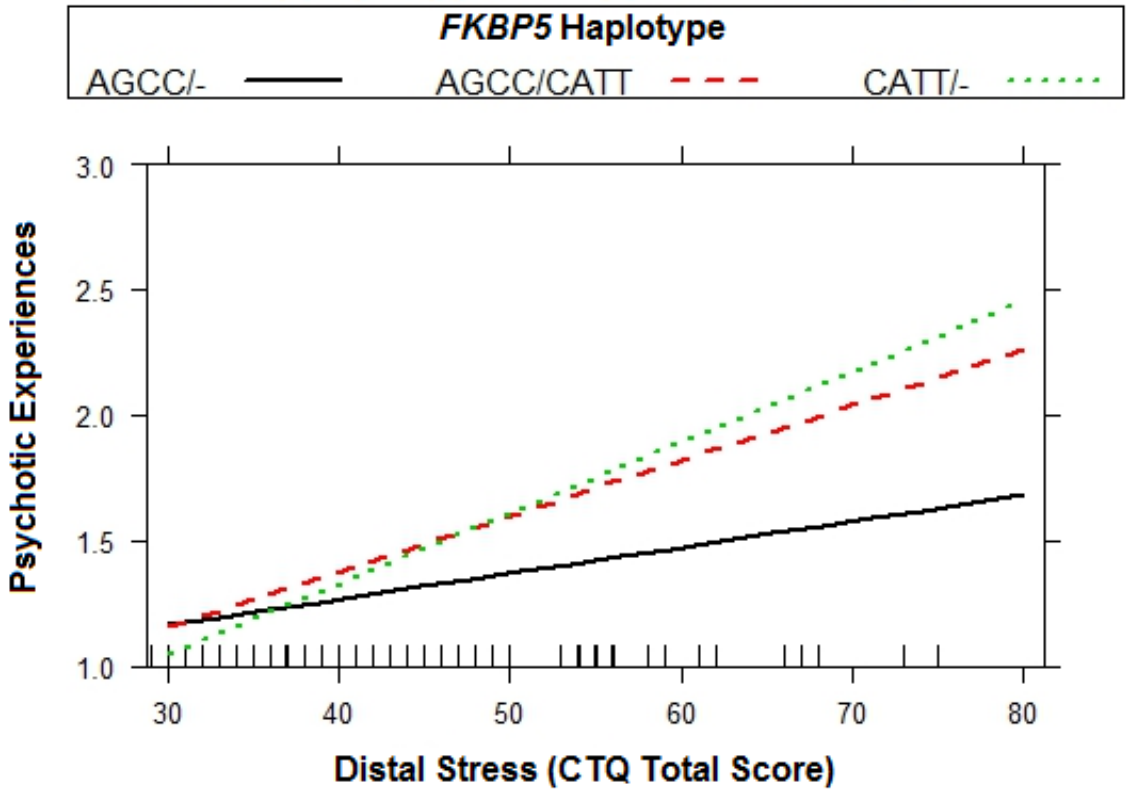
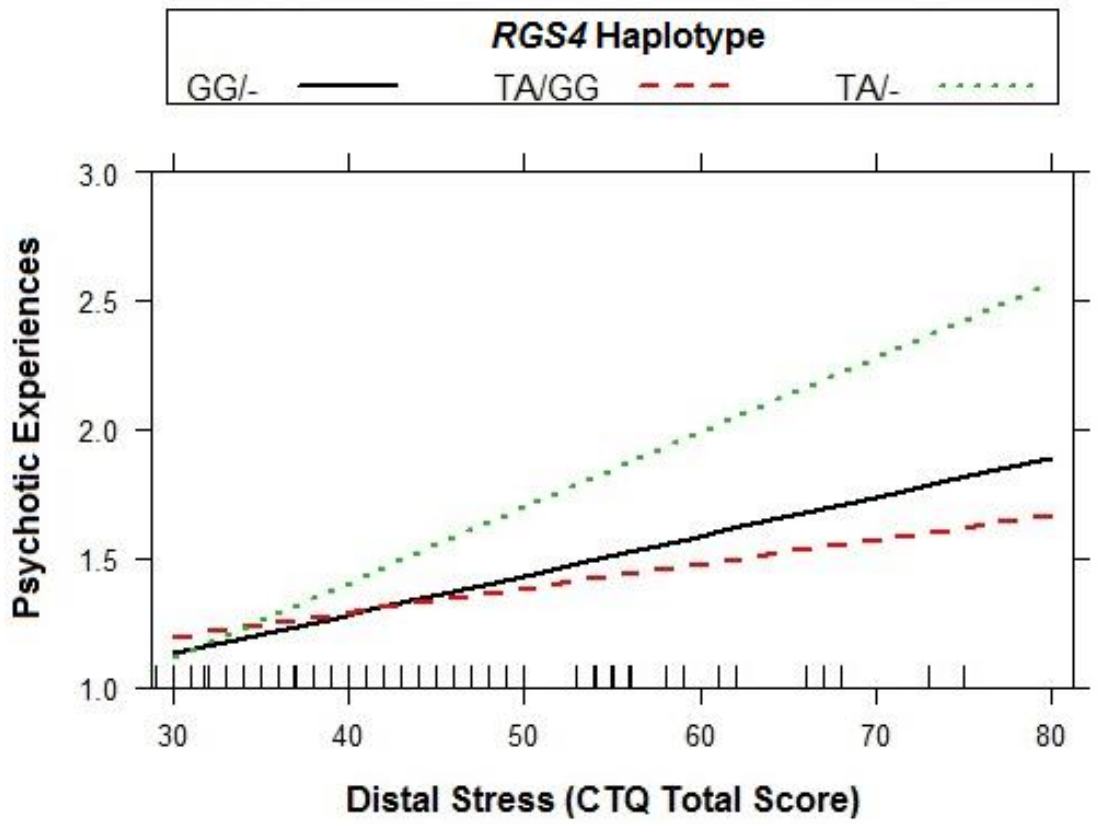
Supplementary material

Figure S1. Interaction between Distal Stress and *FKBP5* haplotype on Psychotic Experiences in the Total Sample (n=309)



Note that the groups for the *FKBP5* haplotype were: 1) carriers of at least one risk haplotype (CATT/-), 2) carriers of one risk haplotype and one protective haplotype (AGCC/CATT), and 3) carriers of at least one protective haptlotype (CATT/-.).

Figure S2. Interaction between Distal Stress and *RGS4* haplotype on Psychotic Experiences in the Total Sample (n=309)



Note that the groups for the *RGS4* haplotype were: 1) carriers of at least one risk haplotype (TA/-), 2) carriers of one risk haplotype and one protective haplotype (TA/GG), and 3) carriers of at least one protective haptlotype (GG/-.).

SECTION 3

GENETIC MODERATION OF

STRESS SENSITIZATION

Chapter 3

The Interaction between Childhood Bullying and the *FKBP5* Gene on Psychotic-Like Experiences and Stress Reactivity in Real Life

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Abstract

Aim: The present study employed Experience Sampling Methodology to examine whether the interaction between childhood bullying and *FKBP5* variability (i) is associated with the expression of psychotic-like experiences, paranoia, and negative affect, and (ii) moderates psychotic-like, paranoid, and affective reactivity to different forms of momentary stress (situational and social) in daily life.

Methods: A total of 206 nonclinical young adults were interviewed for bullying with the Childhood Experience of Care and Abuse and were prompted randomly eight times daily for one week to complete assessments of their current experiences, affect, and stress appraisals. Participants were genotyped for three *FKBP5* single nucleotide polymorphisms (SNPs) (rs3800373, rs9296158, and rs1360780) that have been linked to hypothalamus-pituitary-adrenal axis reactivity. Multilevel analyses were conducted to examine the effect of the interaction between childhood bullying and the *FKBP5* haplotype derived from these three SNPs.

Results: The interaction between bullying and the *FKBP5* haplotype was associated with positive, but not negative, psychotic-like experiences, paranoia, and negative affect. The bullying x *FKBP5* interaction also moderated the association of a social stress appraisal (specifically, being alone because people do not want to be with you) with psychotic-like experiences and negative affect in daily life. Simple slopes analyses indicated that, in all cases, the associations were significantly increased by exposure to bullying in participants with the risk haplotype, but not for those with the non-risk haplotype.

Discussion: The present study provides the first evidence of the interplay between childhood bullying and *FKBP5* variability in the real-world expression of psychosis proneness and social stress reactivity. The findings underscore the importance of investigating how gene-environment

interactions are involved in mechanistic pathways to the extended psychosis phenotype and lend further support to the increasing relevance given to socially defeating appraisals in the experience of reality distortion.

Keywords: FKBP5 gene, bullying, gene x environment interaction, experience sampling methodology; social stress.

Introduction

Mounting evidence indicates that childhood adversity is associated with an increased risk for psychosis phenotypes [1]. The association has been repeatedly observed with psychotic disorders, subclinical psychotic symptoms, and schizotypy traits [2-4]—consistent with converging research supporting the notion of etiological continuity between the clinical and nonclinical manifestations of psychosis [5, 6]. Among different types of interpersonal childhood adversity, experiences within the family milieu have been more extensively studied. However, there is increasing recognition that peer relations are key to children's and adolescent's developmental outcomes [7] and that exposure to bullying by peers can have a host of long-term detrimental effects [8]. Bullying involves intentional aggressive/hostile behavior in the context of actual or perceived imbalance of power [9, 10] and recent findings across different study designs (including prospective studies) and populations have demonstrated its association with psychotic phenomena [11-14].

It has been proposed that exposure to childhood interpersonal adversities may increase the risk for psychosis through a process of behavioral and biological sensitization involving hypothalamus-pituitary-adrenal (HPA) axis dysregulation and contributing to a final common pathway of dopamine sensitization in mesolimbic regions [15]. Dysregulation of the HPA axis involves dysregulation of the hypothalamic peptides of the corticotropin-releasing and arginine vasopressin hormones, resulting in enhanced release of plasma adrenocorticotropic hormone and glucocorticoid cortisol. Glucocorticoids promote the physiological stress response of fight-or-flight and are crucial for terminating the response through a negative feedback loop [16]. Such impaired negative feedback regulation via the glucocorticoid receptor (GR) has been proposed as

a potential risk factor for stress-related psychopathology [16]. A critical regulator of GR activity is the FK506 binding protein 5 (FKBP5), a 51-kDa protein encoded by the *FKBP5* gene (located on chromosome 6p21.31 in humans) [17]. Notably, a functional haplotype that comprises up to 18 single nucleotide polymorphisms (SNPs) in the *FKBP5* gene has been related to increased expression of FKBP5 in response to GR activation and variation in GR sensitivity [16-18]. This haplotype is tagged by three SNPs (rs3800373, rs9296158, and rs1360780) that, for this reason, have been the most studied and characterized *FKBP5* polymorphisms [19]. Several studies pointed out that the risk alleles of these polymorphisms are the C, A, and T alleles, respectively [17]. Research has also suggested that the rs1360780 is the variant most likely conferring the haplotype functionality [17].

An increasing number of gene-environment interaction (GxE) studies have investigated the interaction between psychosocial stressors and *FKBP5* variability, with findings suggesting that adverse childhood experiences in interaction with the above mentioned haplotype are associated with risk for a range of psychopathological phenotypes (for review, see [17]). In this regard, recent studies showed that genetic variation in the *FKBP5* gene interacted with childhood trauma in the expression of psychotic phenomena in clinical and nonclinical samples [20-22]. Nevertheless, to the best of our knowledge, the role of the interaction between *FKBP5* variability and childhood bullying in particular has not been previously investigated.

There are also no GxE studies examining whether the interaction between childhood adverse experiences and *FKBP5* variability plays a role in heightening affective, paranoid, and psychotic-like responses to stress in daily life. Researchers have increasingly employed momentary assessment strategies to examine with ecological validity the experience and expression of psychological constructs in daily life as well as their environmental triggers (e.g.,

[23, 24]). The Experience Sampling Method (ESM) is a within-day self-assessment technique that prompts participants at random intervals to complete brief questionnaires about their current experiences, including stress, cognition, affect, and symptoms. By assessing participants in real time and in their real-life settings, ESM offers several advantages in comparison to traditional assessment techniques. These include the minimization of retrospective bias, enhanced ecological validity, and the ability to capture the context in which experiences occur [23, 25]. ESM measures exhibit good psychometric properties and have proven useful for examining the phenomenology and stress reactivity dynamics of the clinical and subclinical psychosis phenotypes [26-30]. In addition, it has been highlighted that utilizing prospective and repeated assessments of environmental exposures increases precision and reliability in the realm of GxE research [31]. Thus, the features of ESM data should enhance the power and quality of GxE studies and increase mechanistic insights that complement findings from large-scale epidemiological investigations [32-35].

In a previous ESM study we found that bullying was associated with psychotic-like experiences (PLEs) in daily life as well as with increased affective and paranoid reactivity to daily life stressors [36]. However, that study did not examine what factors may interact with bullying in shaping the expression of psychotic phenomena and stress reactivity in daily life. Therefore, the present study sought to examine in a non-clinically ascertained sample of young adults whether the interaction between bullying and *FKBP5* (i) is associated with PLEs, paranoia, and negative affect, and (ii) moderates psychotic-like, paranoid, and affective reactivity to different forms of momentary stress (i.e., situational and social) in daily life. We predicted that the interaction between bullying and the CAT risk haplotype of the *FKBP5* gene would be associated with higher levels of PLEs, paranoia, and negative affect, but not negative-like symptoms. We also expected

that the previously reported association of stress with PLEs, paranoia, and affective experiences in daily life [26], and particularly the association with social stress, would be moderated by the bullying x *FKBP5* interaction, such that the association would be stronger for risk haplotype participants with childhood bullying exposure.

Methods

Ethics Statement

The present study was approved by the Universitat Autònoma de Barcelona Ethics Committee and conformed to the Helsinki Declaration. Participants had full capacity to consent to participation in research and gave written informed consent before taking part in the study.

Participants

The sample forms part of PSYRIS-Barcelona, a longitudinal study examining psychosis risk and resilience. The sample was comprised of 206 nonclinically ascertained young adults from whom usable interview, ESM, and *FKBP5* genotype data were obtained. The participants were drawn from a screening sample of 589 undergraduate students (547 had complete usable data) at the Universitat Autònoma de Barcelona (Spain). Participants with high schizotypy scores were oversampled in order to ensure adequate representation of schizotypy in the current sample. A detailed description of the sample selection procedure has been provided elsewhere [26, 37]. The mean age of the sample was 21.3 years (*SD* = 2.4) and 78.6% were women. Ninety two percent were of European origin (subjects and both parents born in a European country).

Materials and Procedure

Bullying. Questions from the Childhood Experience of Care and Abuse (CECA) [38] were used to assess bullying by peers. The CECA is a retrospective investigator-based interview that measures childhood experiences prior to the age of 17 years. Bullying is scored on a 4-point scale ranging from "marked" to "little/none", based on specific rating rules and benchmarked thresholds. The interviews were conducted by psychologists and advanced graduate students in clinical psychology. Consensus meetings to discuss ratings were held regularly throughout the data collection period. The continuous severity ratings of bullying victimization were used for analyses.

ESM assessments. The ESM data collection was conducted with personal digital assistants (PDAs) that signaled participants randomly 8 times a day (between 10 a.m. and 10 p.m.) for one week to complete short questionnaires. When participants were signaled by the PDA, they had 5 minutes to initiate responding. After this time interval or the completion of the questionnaire, the PDA shut down until the next signal. The full list of ESM items can be found in Barrantes-Vidal et al. [26]. The social contact item was answered dichotmously (alone/with others), whereas the remaining items employed in the present study were answered on 7-point scales from "not at all" to "very much".

ESM measures of symptoms, negative affect, social contact, and stress were used for analyses. Following Barrantes-Vidal et al. [26], we created indices of PLEs (8 items: unusual senses, unusual thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and passivity; alpha index =.74) and paranoia (2 items: feeling suspicious and mistreated; alpha index =.70), and used the experience of diminished thoughts/emotions ("Right now I have no thoughts or emotions") as a

measure of negative-like symptoms. Negative affect was measured by an index composed of 4 items (feeling anxious, sad, angry, and guilty; alpha index =.80). With regard to stress, note that consistent with previous ESM research (e.g., [27, 30, 39, 40]), the present study did not focus on objective environmental stressors but rather on subjective appraisals of stress in daily life. The item "My current situation is stressful" was used to assess situational stress. Regarding social stress appraisals, we distinguished between social stress when participants were alone (assessed by the item "I am alone because people do not want to be with me") and social stress when participants were with others (assessed by 2 items: "I feel close to this person (people)" and "Right now I would prefer to be alone"). Additionally, the social contact item was included in the analyses in order to distinguish the effects of social stress appraisals from the effects of simply being alone or with others at the time of the signal.

Genotyping. Genomic DNA was extracted using the Real Extraction DNA kit (Durviz S.L.U., Valencia, Spain). The three *FKBP5* SNPs rs3800373, rs9296158, and rs1360780 were genotyped using TaqMan 5'-exonuclease allelic discrimination assay (Applied Biosystems, custom assays: C_27489960_10, C_1256775_10, and C_8852038_10, respectively). Minor allele frequencies were 0.34 for rs3800373 (allele C), 0.33 for rs9296158 (allele A), and 0.33 for rs1360780 (allele T). No differences were observed between the allele frequencies in our sample and those reported in European (EUR from 1000 genomes) and Spanish (IBS from HapMap) reference populations ($p > 0.05$). Genotypic frequencies for each polymorphism are reported in Table 1. All SNPs were in accordance with Hardy-Weinberg Equilibrium (all $p > 0.5$).

Linkage disequilibrium, which is the tendency of SNPs to be inherited together, was examined by pair-wise comparisons of r^2 and D'using Haploview version 4.2 [41]. The three studied SNPs were observed to be in high linkage disequilibrium (D'=0.89). Haplotypes

considering these three polymorphisms were estimated using a bayesian approach implemented with PHASE software [42]. The frequencies of the CAT (risk haplotype) and the AGC (non-risk haplotype) were 0.29 and 0.62, respectively. For analyses, participants were classified in two groups: i) risk carriers, which included carriers of at least one risk haplotype (i.e., CAT/CAT, CAT/XXX, or CAT/AGC), and ii) non-risk carriers, which included non-carriers of the risk haplotype (i.e., AGC/AGC, AGC/XXX, or XXX/XXX) (Table 1).

Statistical Method

ESM data have a hierarchical structure in which ESM ratings (level 1 data) are nested within participants (level 2 data). Multilevel or hierarchical linear modeling provides a more appropriate method than conventional unilevel analyses for analyzing nested data and is standard for the analysis of ESM data [43, 44].

Two types of multilevel analyses were conducted in the present study. First, in order to examine the impact of the interaction of bullying and *FKBP5* on PLEs, paranoia, and negative affect in daily life, we assessed the independent effect of level 2 predictors (bullying, *FKBP5*, and the bullying x *FKBP5* interaction) on level 1 dependent measures (ESM ratings in daily life). Note that as described above we have already reported the association of bullying with ESM ratings in a study examining a wide variety of adversity exposures on daily-life experiences [36]; therefore, the main effects of bullying are not the object of the current study and will be solely described as a necessary step required to yield the GxE interaction. Second, to analyze whether the bullying x *FKBP5* interaction moderates the association of momentary stress with experiences in daily life, cross-level interactions (or slopes-as-outcomes) were computed. Cross-level interactions were used to examine whether level 1 relationships (e.g., the association between feeling unwanted and

PLEs in daily life) vary as a function of level 2 variables (e.g., the bullying x *FKBP5* interaction). In both the analyses of direct effects and cross-level interactions, the effect of bullying and the *FKBP5* haplotype were examined separately (i.e., two separate models were used, one in which bullying was the predictor and another in which the *FKBP5* haplotype was the predictor).

In order to examine the effect of the bullying x *FKBP5* interaction, bullying, the *FKBP5* haplotype, and the interaction term were entered simultaneously in the same model. When a significant bullying x *FKBP5* interaction was found, the effect of the interaction was examined within each haplotype group using simple slopes. The multilevel analyses were computed with MPlus 6 [45]. Graphics and simple slopes were computed with HLM 7.01 program [46]. Level 1 predictors were group mean centered and level 2 predictors were grand mean centered. The data departed from normality in some cases, so parameter estimates were calculated using robust standard errors. Furthermore, level 1 criteria exhibiting significant skew were treated as categorical.

Results

Participants completed an average of 40.8 usable ESM questionnaires (*SD* = 9.1). The *FKBP5* risk haplotype and bullying were not correlated ($r = 0.08$) and neither was associated with the number of usable records ($r = 0.03$ and -0.04, respectively). Additionally, there were no sex differences in either variable (bullying: $t = 0.849$, $p = 0.397$; *FKBP5* haplotype: $\chi^2 = 1.658$, $p = 0.198$).

As shown in Table 2, bullying was associated with PLEs and negative affect but not with paranoia or negative-like symptoms. The *FKBP5* haplotype was not associated with daily life symptoms or negative affect. The interaction of bullying and the *FKBP5* haplotype was

significantly associated with PLEs, paranoia, and negative affect. Simple slopes analyses indicated that, as expected, bullying increased PLEs and paranoia for participants with the risk haplotype (0.059, *SE* = 0.021, *t* = 2.78, *p* < 0.01; 0.085, *SE* = 0.035, *t* = 2.41, *p* < 0.05, respectively), but not for those with the non-risk haplotype (0.002, *SE* = 0.019, *t* = 0.08, ns; -0.018, *SE* = 0.031, *t* = -0.58, ns, respectively). Similarly, bullying was associated with increased negative affect for participants with the risk haplotype (0.188, *SE* = 0.051, *t* = 3.72, *p* < 0.001), but not for those with the non-risk haplotype (0.037, *SE* = 0.058, *t* = 0.64, ns).

Cross-level interaction analyses examined whether bullying, the *FKBP5* haplotype, and their interaction moderated the association of social contact and stress appraisals with PLEs, paranoia, and negative affect in daily life (Table 3). Bullying moderated the association of situational stress and preference to be alone with paranoia. It also moderated the association of social contact with PLEs and that of decreased social closeness with negative affect. The *FKBP5* haplotype did not moderate the associations of situational stress or social stress with experiences in daily life. The bullying x *FKBP5* interaction moderated the association of feeling unwanted when alone and PLEs in daily life. Simple slopes analyses indicated that the association between feeling unwanted and PLEs was significantly increased by exposure to bullying in participants with the risk haplotype (0.056, *SE* = 0.027, *t* = 2.07, *p* < 0.05; see Fig 1), but not for those with the non-risk haplotype (-0.034, *SE* = 0.020, *t* = -1.74, ns).

The bullying x *FKBP5* interaction also moderated the association of feeling unwanted with negative affect. Simple slopes analyses showed that the association between this appraisal and negative affect was significantly increased by exposure to bullying in risk haplotype participants (0.144, *SE* = 0.051, *t* = 2.80, *p* < 0.01; see Fig 2), but not in non-risk haplotype participants (-0.092, *SE* = 0.075, *t* = -1.23, ns).

Additional Analyses

Following the recommendation of a reviewer, we performed exploratory analyses partialing out the CECA parental antipathy ratings to examine whether the effects of the bullying x *FKBP5* interaction on daily life outcomes were found over-and-above the effects of another form of childhood maltreatment. Specifically, we partialed the parental antipathy score out of the main effects of bullying and *FKBP5*, and the antipathy rating and the antipathy x bullying and antipathy x *FKBP5* interaction out of the analysis of the bullying x *FKBP5* interaction. This followed the reviewer's suggestion that we select a single CECA exposure to use as a confounding measure. For this sample CECA parental antipathy and role reversal exposures were available (peak rating taking into account behavior of mother and father figure). We selected parental antipathy because (i) it shares similarities with peer bullying (e.g., involving rejection, coldness, hostility) and (ii) it is carried out by different figures than peer bullying. Note that parental antipathy had a modest (although not significant) correlation with bullying in our sample (r=.13) – making it an ideal covariate. This method follows recommendations by Keller [47], who suggested that in order to properly control for potential confounders, all the covariate-by-environment and the covariate-by-gene interaction terms should be entered in the same model that tests the gene-by-environment interaction term. However, it should be interpreted cautiously in the current study because of the post hoc nature of the analyses and the lack of a priori selection of parental antipathy. We reran all of the analyses in Tables 1 and 2 using this strategy. The results were largely unchanged (see supplemental Tables S1 and S2). All the significant bullying x *FKBP5* interactions remained, and the association between situational stress and paranoia became significantly moderated by the bullying x *FKBP5* interaction. Simple slopes indicated that the association was significantly increased by exposure to bullying in participants with the risk haplotype (0.044, *SE*= 0.018, *t*=

2.46, $p < 0.05$), but not for those with the non-risk haplotype (0.007, *SE*= 0.014, *t*= 0.48, ns). These additional analyses add support to the interpretation that the bullying x *FKBP5* effects are robustly significant and attributable to this particular type of adversity.

Discussion

To the best of our knowledge, the current study is the first to examine the interplay between bullying and *FKBP5* variability in the expression of psychotic phenomena and stress reactivity in the realm of daily life. The results indicated that the interaction between bullying and the risk *FKBP5* haplotype was associated with PLEs, paranoia, and negative affect, and that it moderated psychotic-like and affective reactivity to a social stress appraisal (i.e., feeling unwanted by others) in a nonclinical sample. This work expands on previous GxE research supporting that the interaction between *FKBP5* variability and childhood adversity exposure increases the risk for psychosis phenotypes. The findings contribute to our understanding of how the complex interplay between genetic and environmental factors is involved in the real-world expression of psychosis proneness.

The results regarding the interaction between bullying and *FKBP5* variability on psychotic-like, paranoid, and affective experiences were in line with our hypotheses and provide evidence of a GxE interaction on subclinical psychotic phenomena in real life. Furthermore, the finding that the interaction was not associated with negative-like symptoms is consistent with the contention that positive and negative psychotic features may involve different etiological pathways [48], with environmental adversity exposures and biological mechanisms involved in regulating the stress response thought to be particularly relevant for the positive symptom dimension (e.g., [15]).

Prior research has consistently shown that exposure to interpersonal childhood adversities increases the risk for several psychopathological phenotypes in carriers of the functional haplotype associated with higher FKBP5 induction and prolonged cortisol responses [17]. Although next-generation sequencing projects have enabled to catalogue the broad range of variants in the *FKBP5* gene (e.g., [49]), the majority of these studies have investigated *FKBP5* variability using a tagging approach and focusing on some of the most common tag SNPs (rs3800373, rs9296158, or rs1360780) of this haplotype [18]. However, the investigated SNPs have not been the same in all studies and, to our knowledge, there are no studies examining specifically the role of the haplotype comprised by these three tag SNPs on psychosis proneness. Nevertheless, the finding that the bullying and *FKBP5* interaction was associated with positive psychotic phenomena is consistent with a recent study showing that childhood abuse was associated with increased PLEs in carriers of the risk alleles of rs1360780 in a nonclinical sample [22]. Our results are also in agreement with the first study examining the role of *FKBP5* in psychosis [20], which found that carriers of the rs1360780 and rs9296158 risk alleles (as well as rs1043805, which was not investigated here) were more vulnerable to the effect of childhood trauma on PLEs in a general population sample. In the same study, they also found that rs9296158 moderated the effect of trauma on psychotic symptoms in patients with a psychotic disorder. Of note, neither our study nor previous ones in nonclinical and clinical samples [20-22, 50] found that *FKBP5* variability by itself was associated with positive psychotic phenomena or presence of a psychotic disorder. Therefore, taken together, findings are in line with the notion that the contribution of *FKBP5* variability to psychosis risk may be dependent upon the presence of specific environmental exposures [51].

The finding that the association of the risk alleles of the haplotype with psychotic phenomena is commonly triggered by exposure to childhood adversity is interesting in light of

recent molecular studies suggesting that childhood trauma exposure could induce allele-specific epigenetic modifications that may increase the risk for stress-related phenotypes [52]. Specifically, Klengel et al. [52] found that childhood abuse exposure was associated with preferential demethylation of DNA (near a glucocorticoid response element in *FKBP5*) in risk allele carriers, which enhances differences in glucocorticoid receptor sensitivity and entails a dysregulation of the stress system that may eventually increase vulnerability for certain psychopathological phenotypes. Importantly, this reduced methylation seemed to be dependent specifically on childhood abuse exposure, but not adult trauma exposure or current levels of cortisol, indicating that there may be a critical developmental stage for such epigenetic effects [52].

Regarding stress reactivity, we found that the GxE interaction moderated the association of appraisals of being unwanted when alone with PLEs and negative affect. In particular, our results indicated that these associations were significantly increased by exposure to bullying in risk haplotype participants, but not in non-risk haplotype participants. By contrast, the interaction did not moderate affective and symptomatic reactivity to situational stress and other forms of social stress (i.e., appraisals of diminished closeness and increased preference for being alone). In light of these results, it is attractive to speculate that social defeat is a mechanism involved in increasing reactivity in individuals with the risk haplotype.

More specifically, it has been suggested that childhood adversity may increase psychosis vulnerability by inducing a state of social defeat, characterized by feelings of outsider status and decreased self-value [53, 54]. Of note, recent research has indicated that social defeat plays a mediating role in the association between childhood trauma and psychotic phenotypes at the population level [55], and that a history of social defeat increases the likelihood of psychotic responses during social interactions in an experimental social environment generated by Virtual

Reality in clinically at-risk individuals [56]. Bullying has been conceptualized as a socially defeating experience and its parallels with animal models of social defeat have been highlighted [57]. Likewise, the appraisal of being alone because others do not want to be with you could be considered a proximal micro-level experience of social defeat. Previous work indicated that mice lacking the *FKBP5* gene showed decreased neuroendocrine/physiological responses to chronic social defeat stress (as compared with wild-type animals), pointing to an increased glucocorticoid negative feedback of the HPA axis that may be modulated by heightened GR sensitivity [58]. Such findings support human studies suggesting that *FKBP5* risk alleles may increase sensitivity to psychosocial adversities through an enhanced FKBP5 expression and thereby diminished GR sensitivity [16, 17]. In this context, our results may therefore suggest that the *FKBP5* risk haplotype amplifies the likelihood that distal experiences of social defeat will increase psychotic-like reactivity to proximal socially defeating appraisals.

Strengths of the present study include the use of an interview measure to assess bullying, which allowed to obtain in-depth information and minimize biases related to subjective responding [59]. The estimation of the risk haplotype is also a strength given that it reports the full variability of a DNA fragment and increases the power to find genetic associations [60]. In addition, we employed ecologically valid measures of experiences obtained prospectively and repeatedly during a one-week period, increasing the power and reliability of GxE research [31, 32]. Finally, although we computed multiple analyses, they were limited to a priori goals and hypotheses of the study to avoid exploratory analyses that would increase the risk of Type I error. Also, following the suggestion of a reviewer, we confirmed that the findings reported remain largely unchanged after partialing out the effect of another type of adversity (parental antipathy), which strengthens the role of bullying as a relevant exposure. Limitations of the study include the cross-sectional

nature of the data, which limits interpretations about the causal effects of GxE interactions. Similarly, given that predictor and criterion ESM variables were measured concurrently, causal inferences regarding the effects of stress appraisals cannot be definitively made. Furthermore, the generalizability of the present results is limited by the use of a predominantly female university student sample. Future studies should investigate at-risk and clinical samples to identify whether the interaction between bullying and *FKBP5* variability is relevant across the psychosis continuum. Likewise, further research may consider assessing whether the direct and cross-level effects reported in the current study are found over-and-above the effects of other childhood adversity exposures.

To conclude, the present study provides a novel contribution by showing that bullying and the *FKBP5* risk haplotype interact in shaping the expression of reality distortion and social stress reactivity in real life. The current study concurs with and expands previous work by providing evidence supporting the 3-hit [51] and sensitization [15] hypotheses, that is, the relevance of the interaction of 1) genetic risk, 2) distal environmental factors and 3) proximal environmental re-exposures on the expression of psychosis proneness. Our findings highlight that examining the interplay between genetic and environmental factors should increase our understanding of the mechanistic pathways leading to the extended psychosis phenotype and further support the increasing relevance given to socially defeating appraisals in the experience of reality distortion.

Table 1. Description of the *FKBP5* Single Nucleotide Polymorphisms (SNPs) and Haplotype Groups (n=206)

SNPs	**Frequencies**		**Empirical background**[a]	
Reference sequence (rs)	Genotypes	n (%)	Risk allele	Non-risk allele
rs3800373	C/C	24 (11.6%)	C	A
	A/C	92 (44.7%)		
	A/A	90 (43.7%)		
rs9296158	A/A	21 (10.2%)	A	G
	G/A	94 (45.6%)		
	G/G	91 (44.2%)		
rs1360780	T/T	24 (11.7%)	T	C
	C/T	88 (42.7%)		
	C/C	94 (45.6%)		
Haplotype groups (n)	Haplotypic combinations	n (%)	Risk haplotype	Non-risk haplotype
Risk carriers (n=102)	CAT/CAT or CAT/XXX[c]	24 (11.6%)	CAT	AGC
	CAT/AGC	78 (37.9%)		
Non-risk carriers[b] (n=104)	AGC/AGC or AGC/XXX[c]	98 (47.6%)		
	XXX/XXX[c]	6 (2.9%)		

[a] Risk and non-risk alleles according to Zannas and Binder [17].

[b] Note that CAT/AGC combination has been included in the "risk carriers" group.

[c] XXX = Other haplotype combinations (AAC, AAT, CGC, CGT, CAC, or AGT).

Table 2. Main Effects of Bullying, the *FKBP5* Haplotype, and their Interaction on Psychosis Spectrum Experiences and Negative Affect (n=206)

Level 1 Criterion	**Level 2 Predictors**		
	Bullying	*FKBP5*	Bullying x *FKBP5*[b]
	γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychosis Spectrum			
Psychotic-like index	0.034 (SE=0.015)*	-0.008 (SE=0.022)	0.027 (SE=0.013)*
Paranoia index	0.038 (SE=0.026)	-0.053 (SE=0.047)	0.048 (SE=0.022)*
No thoughts/emotions[a]	0.289 (SE=0.168)	-0.299 (SE=0.329)	0.199 (SE=0.162)
Affect			
Negative affect index	0.113 (SE=0.040)**	-0.128 (SE=0.067)	0.071 (SE=0.036)*

*p <.05, **p <.01, ***p < .001.

[a] Item was run as categorical.

[b] Bullying and *FKBP5* were examined independently. The interaction was examined with bullying and *FKBP5* in the model.

Table 3. Cross-Level Interactions with Bullying, the *FKBP5* Haplotype, and the Bullying x *FKBP5* Interaction (n=206)

Level 1 Criterion	**Level 1 Predictor**[a]		**Level 2 Predictors**		
			Bullying	*FKBP5*	Bullying x *FKBP5*[b]
	γ_{10} (*df*=204)		γ_{11} (*df*=204)	γ_{11} (*df*=204)	γ_{13} (*df*=202)
Psychotic-like index	Situation stressful	0.035 (SE=0.004)***	0.006 (SE=0.006)	0.002 (SE=0.009)	0.004 (SE=0.005)
Paranoia index	Situation stressful	0.078 (SE=0.009)***	0.029 (SE=0.012)*	0.015 (SE=0.020)	0.017 (SE=0.011)
Negative affect index	Situation stressful	0.215 (SE=0.012)***	0.015 (SE=0.012)	-0.001 (SE=0.023)	0.005 (SE=0.012)
Psychotic-like index	Alone	0.000 (SE=0.006)	-0.015 (SE=0.006)*	-0.008 (SE=0.012)	-0.006 (SE=0.005)
Paranoia index	Alone	-0.008 (SE=0.014)	0.001 (SE=0.014)	-0.030 (SE=0.028)	-0.001 (SE=0.014)
Negative affect index	Alone	-0.046 (SE=0.018)*	0.012 (SE=0.018)	0.042 (SE=0.035)	0.015 (SE=0.018)
Psychotic-like index	Alone b/c not wanted	0.083 (SE=0.018)***	0.019 (SE=0.023)	0.001 (SE=0.040)	0.037 (SE=0.016)*
Paranoia index	Alone b/c not wanted	0.150 (SE=0.048)**	0.039 (SE=0.053)	-0.029 (SE=0.108)	0.054 (SE=0.044)
Negative affect index	Alone b/c not wanted	0.170 (SE=0.046)***	0.075 (SE=0.044)	0.150 (SE=0.104)	0.104 (SE=0.044)*
Psychotic-like index	Close to other	-0.009 (SE=0.003)**	-0.004 (SE=0.003)	0.005 (SE=0.005)	-0.002 (SE=0.003)
Paranoia index	Close to other	-0.027 (SE=0.008)***	-0.017 (SE=0.009)	0.016 (SE=0.015)	-0.005 (SE=0.008)
Negative affect index	Close to other	-0.048 (SE=0.009)***	-0.022 (SE=0.009)*	0.008 (SE=0.017)	-0.001 (SE=0.009)
Psychotic-like index	Prefer to be alone	0.020 (SE=0.004)***	0.004 (SE=0.005)	0.009 (SE=0.009)	0.004 (SE=0.004)
Paranoia index	Prefer to be alone	0.070 (SE=0.010)***	0.028 (SE=0.014)*	0.007 (SE=0.022)	0.019 (SE=0.012)
Negative affect index	Prefer to be alone	0.126 (SE=0.013)***	0.024 (SE=0.014)	-0.012 (SE=0.026)	0.013 (SE=0.013)

*p <.05, **p <.01, ***p < .001.

[a] Note that the statistical significance of the associations of the level 1 predictor and criterion did not vary across each level 2 predictor. The table reports the coefficient of the association of the level 1 predictor and criterion for the analyses of bullying.

[b] Bullying and *FKBP5* were examined independently. The interaction was examined with bullying and *FKBP5* in the model.

Fig 1. Association between feeling unwanted and PLEs across levels of bullying in *FKBP5* risk-haplotype participants.

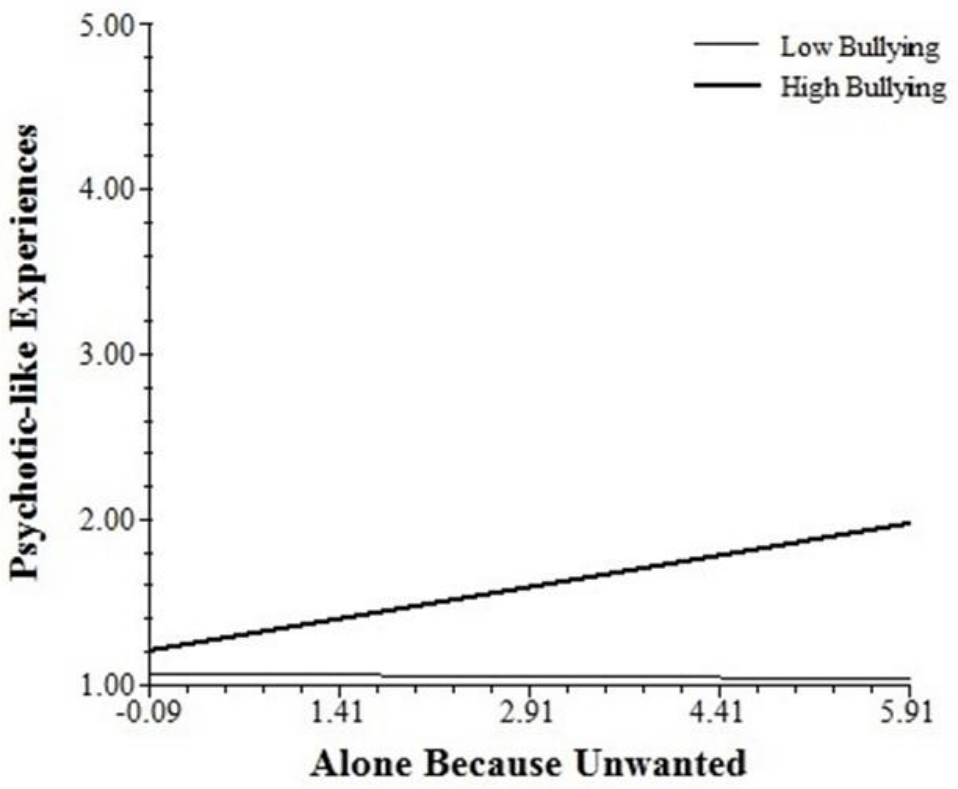
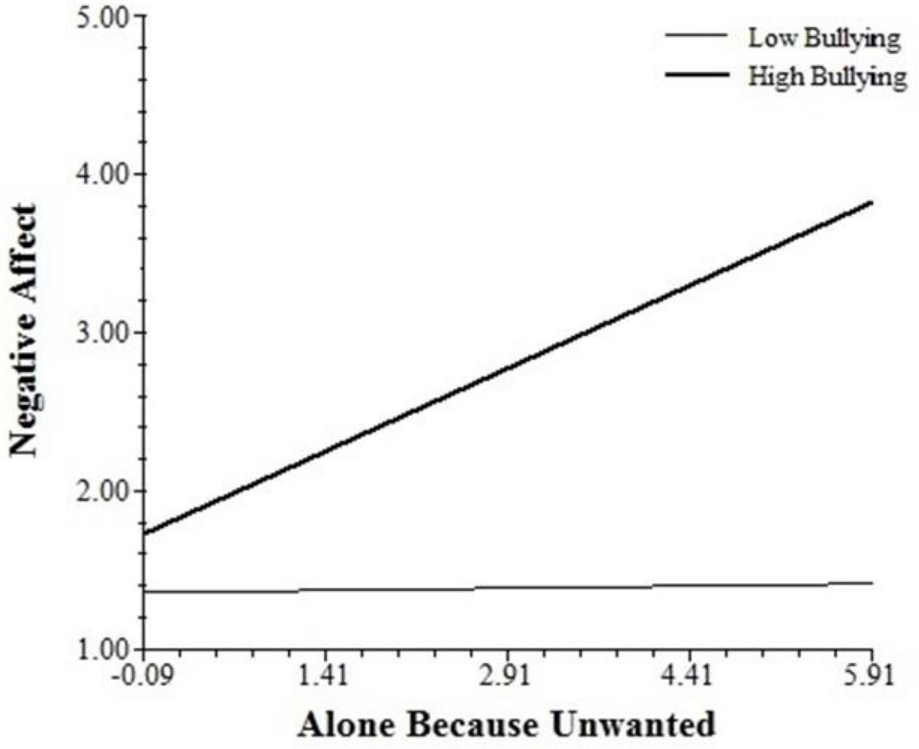


Fig 2. Association between feeling unwanted and negative affect across levels of bullying in *FKBP5* risk-haplotype participants.



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Supplementary material

Table S1. Main Effects of Bullying, the *FKBP5* Haplotype, and their Interaction on Psychosis Spectrum Experiences and Negative Affect Partialing out the Effects of Parental Antipathy (n=206).

Level 1 Criterion			**Level 2 Predictors**				
	Bullying[b]	Parental Antipathy[b]	*FKBP5*[b]	Parental Antipathy[b]	Antipathy x Bullying[c]	Antipathy x *FKBP5*[c]	Bullying x *FKBP5*[c]
	γ_{01} (*df*=203)	γ_{02} (*df*=203)	γ_{01} (*df*=203)	γ_{02} (*df*=203)	γ_{04} (*df*=199)	γ_{05} (*df*=199)	γ_{06} (*df*=199)
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Psychosis Spectrum							
Psychotic-like index	0.032 (0.012)*	0.021 (0.014)	-0.009 (0.022)	0.025 (0.013)	-0.021 (0.012)	-0.007 (0.011)	0.030 (0.014)*
Paranoia index	0.030 (0.028)	0.063 (0.031)*	-0.056 (0.047)	0.068 (0.030)*	-0.042 (0.024)	-0.024 (0.024)	0.053 (0.022)*
No thoughts/emotions[a]	0.281 (0.173)	0.067 (0.170)	-0.309 (0.332)	0.114 (0.170)	-0.083 (0.181)	0.095 (0.188)	0.201 (0.175)
Affect							
Negative affect index	0.107 (0.041)*	0.049 (0.040)	-0.131 (0.067)	0.064 (0.039)	-0.050 (0.033)	0.001 (0.033)	0.076 (0.036)*

*p <.050, **p <.010, ***p < .001. [a] Item was run as categorical. [b] The parental antipathy rating was partialed out of the main effects of bullying and *FKBP5*, which were examined independently. [c] In order to examine the effect of the bullying x *FKBP5* interaction, all simple effects (bullying, *FKBP5* haplotype, parental antipathy) and interaction effects between the covariate and the genetic and environmental variables (antipathy x bullying and antipathy x *FKBP5* haplotype) were entered in the same model.

Table S2. Cross-Level Interactions with Bullying, the *FKBP5* Haplotype, and the Bullying x *FKBP5* Interaction Partialing out the Effects of Parental Antipathy (n=206).

Level 1 Criterion	**Level 1 Predictor**[a]				**Level 2 Predictors**				
Indices			Bullying[b]	Parental Antipathy[b]	*FKBP5*[b]	Parental Antipathy[b]	Antipathy x Bullying[c]	Antipathy x *FKBP5*[c]	Bullying x *FKBP5*[c]
	γ_{10} (*df*=203)		γ_{11} (*df*=203)	γ_{12} (*df*=203)	γ_{11} (*df*=203)	γ_{12} (*df*=203)	γ_{14} (*df*=199)	γ_{15} (*df*=199)	γ_{16} (*df*=199)
			Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Psychotic-like	Situation stressful	0.035 (0.004)***	0.005 (0.006)	0.007(0.005)	0.001 (0.008)	0.008 (0.005)	-0.005 (0.006)	0.002 (0.004)	0.005 (0.004)
Paranoia	Situation stressful	0.078 (0.009)***	0.028 (0.013)*	0.008 (0.013)	0.014 (0.020)	0.012 (0.012)	-0.027 (0.011)*	0.007 (0.011)	0.021 (0.010)*
Negative affect	Situation stressful	0.215 (0.012)***	0.014 (0.012)	0.006 (0.012)	-0.002 (0.023)	0.008 (0.012)	-0.010 (0.011)	0.013 (0.011)	0.005 (0.012)
Psychotic-like	Alone	0.000 (0.006)	-0.015 (0.006)*	0.005 (0.008)	-0.008 (0.012)	0.004 (0.008)	-0.008 (0.005)	0.010 (0.006)	-0.007 (0.005)
Paranoia index	Alone	-0.008 (0.014)	-0.002 (0.015)	0.029 (0.017)	-0.030 (0.027)	0.029 (0.016)	-0.024 (0.012)*	-0.003 (0.015)	0.001 (0.014)
Negative affect	Alone	-0.046 (0.018)*	0.009 (.019)	0.024 (0.019)	0.041 (0.035)	0.025 (0.018)	0.007 (0.016)	0.021 (0.018)	0.010 (0.019)
Psychotic-like	Alone b/c not wanted	0.085 (0.019)***	0.020 (0.023)	-0.011 (0.021)	0.002 (0.039)	-0.010 (0.021)	-0.004 (0.017)	0.006 (0.013)	0.039 (0.017)*
Paranoia index	Alone b/c not wanted	0.145 (0.047)**	0.038 (0.054)	0.019 (0.062)	-0.032 (0.110)	0.024 (0.063)	-0.008 (0.045)	-0.042 (0.053)	0.055 (0.045)
Negative affect	Alone b/c not wanted	0.168 (0.051)**	0.074 (0.043)	0.009 (0.050)	0.149 (0.102)	0.010 (0.052)	0.055 (0.041)	-0.053 (0.044)	0.100 (0.042)*
Psychotic-like	Close to other	-0.009 (0.003)**	-0.003 (0.003)	-0.004 (0.003)	0.006 (0.005)	-0.004 (0.003)	0.002 (0.002)	0.000 (0.003)	-0.002 (0.003)
Paranoia index	Close to other	-0.027 (0.007)***	-0.016 (0.009)	-0.001 (0.010)	0.017 (0.015)	-0.004 (0.010)	0.000 (0.007)	-0.005 (0.008)	-0.004 (0.008)
Negative affect	Close to other	-0.048 (0.009)***	-0.022 (0.010)*	-0.001(0.008)	0.009 (0.017)	-0.004 (0.008)	-0.003 (0.007)	0.004 (0.007)	-0.001 (0.010)
Psychotic-like	Prefer to be alone	0.020 (0.004)***	0.004 (0.005)	0.006 (0.005)	0.008 (0.009)	0.006 (0.005)	-0.003 (0.004)	0.003 (0.004)	0.004 (0.004)
Paranoia index	Prefer to be alone	0.069 (0.010)***	0.026 (0.014)	0.022 (0.013)	0.003 (0.022)	0.024 (0.013)	-0.003 (0.012)	0.001 (0.010)	0.019 (0.012)
Negative affect	Prefer to be alone	0.126 (0.013)***	0.024 (0.014)	0.001 (0.013)	-0.013 (0.026)	0.003 (0.013)	-0.008 (0.011)	0.010 (0.011)	0.013 (0.013)

*p <.050, **p <.010, ***p < .001. [a] Note that the statistical significance of the associations of the level 1 predictor and criterion did not vary across each level 2 predictor. The table reports the coefficient of the association of the level 1 predictor and criterion for the analyses of bullying. [b] The parental antipathy rating was partialed out of the main effects of bullying and *FKBP5*, which were examined independently. [c] In order to examine the effect of the bullying x *FKBP5* interaction, all simple effects (bullying, *FKBP5* haplotype, antipathy) and interaction effects between the covariate and the genetic and environmental variables (antipathy x bullying and antipathy x *FKBP5* haplotype) were entered in the same model.

Chapter 4

Interplay between childhood trauma, *COMT* and *OXTR* genes on psychotic-like reactivity in real life

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Abstract

Gene-environment interaction models suggest that childhood trauma and genetic risk factors may interact to increase vulnerability for psychosis. The current study investigated whether the interaction of childhood trauma with genetic variation in the *COMT* and *OXTR* genes is associated with (i) psychotic-like experiences, paranoia, and negative affect, and (ii) psychotic-like, paranoid, and affective reactivity to social stress. We used the experience sampling method for a one-week period to assess negative affect, symptoms, and social stress appraisals in 206 nonclinical young adults. Participants also completed the Childhood Trauma Questionnaire-Short Form and were genotyped for two single nucleotide polymorphisms in the *COMT* (rs4680) and *OXTR* (rs53576) genes. The results showed that the gene-environment interactions were not directly associated with symptoms or negative affect in daily life; however, they were associated with increased affective and/or psychotic-like reactivity to social stress. Specifically, the interaction between childhood trauma and the number of *COMT* Met alleles moderated the association between preference to be alone and psychotic-like experiences. The interaction of childhood trauma with the number of *OXTR* G alleles moderated the associations of diminished social closeness and preference to be alone with negative affect. Furthermore, the interaction of childhood trauma with the combined action of *COMT* and *OXTR* variation (i.e., number of Met and G alleles) moderated the associations of diminished social closeness and preference to be alone with negative affect and psychotic-like experiences. The study provides a novel contribution by showing that the expression of subclinical psychotic experiences may involve the interplay of distal and proximal stress experiences with variation in genes involved in the dopaminergic and oxytocinergic systems.

Keywords: gene-environment, childhood trauma, *OXTR* rs53576, *COMT* Val158Met, experience sampling, ecological validity, psychotic-like experiences, negative affect.

Introduction

In recent years, gene-environment interaction (GxE) research has indicated that psychosocial adversities (such as childhood trauma) and genetic risk factors may act synergistically to increase vulnerability towards psychotic features (Collip et al., 2013). Consistent with the hypothesis of etiological continuity across personality, subclinical, and clinical expressions of the schizophrenia spectrum, the synergistic effect of environmental and genetic risk factors has been documented for schizotypy traits, subclinical psychotic symptoms, and frank psychosis (e.g., van Nierop et al., 2013; Uher et al., 2014; Barrantes-Vidal et al., 2015). One way in which such factors might interact across development to increase vulnerability is through enhancing stress reactivity—a process that has been suggested to lie on the pathway to the positive dimension of the extended psychosis phenotype (Collip et al., 2008; van Winkel et al., 2008a). Experience Sampling Methodology (ESM; a structured diary technique that assesses participants in real-time and real-life) is a particularly useful tool for investigating mechanistic processes associated with stress reactivity as well as for increasing precision and reliability in the context of GxE research (e.g., Myin-Germeys et al., 2009; van Winkel et al., 2014). Although previous ESM studies have examined whether childhood trauma (Lardinois et al., 2011; Cristóbal-Narváez et al., 2016) and genetic variation (van Winkel et al., 2008b; Collip et al., 2011) are associated with affective and psychotic reactivity to stress, research investigating the impact of the interaction between these factors remains scarce.

Among the neural mechanisms underlying stress sensitization and the emergence of psychosis, the synergistic relation between the hypothalamus-pituitary-adrenal (HPA) activity and dopamine circuitry has received particular attention. Specifically, the diathesis-stress model suggests that the HPA axis may precipitate a cascade of events that leads to aberrant neural circuit

changes, including an abnormal increase in dopamine signaling (Walker and Diforio, 1997; Holtzman et al., 2013; Mizrahi, 2016). For example, several studies have shown that glucocorticoid secretion increases dopamine activity in several brain regions, particularly in mesolimbic regions (Dallman et al., 2004; Marinelli et al., 2006; Arnsten, 2011). This is in line with the dopamine hypothesis of schizophrenia, which postulates that dopamine hyperactivity in the mesolimbic pathway represents a neurochemical abnormality underpinning positive symptoms (Laruelle and Abi-Dargham, 1999; Howes and Kapur, 2009). In light of these findings, dopamine-related genes have been extensively studied in schizophrenia, particularly genes encoding for dopamine receptors and dopamine-metabolizing enzymes such as the catechol-O-methyltransferase (*COMT*). The gene encoding for COMT is located on chromosome 22q11.2 and inactivates catecholamines at postsynaptic sites in the human brain, especially in the prefrontal cortex. The functional polymorphism *COMT* Val158Met involves a guanine (G) to adenine (A) substitution at codon 158, which results in an amino acid change from valine (Val) to methionine (Met) (Lotta et al., 1995). This implies a conformational protein change leading to low thermal stability of COMT protein, and thus decreased enzymatic activity and higher dopamine levels for Met allele carriers (Chen et al., 2004). This has been related to increased brain activity in the ventrolateral prefrontal cortex, hippocampus, and amygdala (Smolka et al., 2005; Drabant et al., 2006) as well as improved cognitive performance (Rosa et al., 2004; Basterra et al., 2012). However, conflicting results have been reported in studies examining the role of *COMT* Val158Met in relation to risk for psychosis phenotypes (Costas et al. 2011). Whereas earlier studies revealed an association between the Met allele and psychotic spectrum symptoms (e.g., Park et al., 2002), later studies found an association with the Val allele (e.g., Wonodi et al., 2003) or no evidence for this association (e.g., Fan et al., 2005).

Several GxE studies have found a pleiotropic effect of the *COMT* Val158Met genotype (Mier et al., 2010). While Val allele carriers seem to present more stress-resistance at the cost of worse cognitive task performance, Met allele carriers tend to display more sensitivity to stress but better cognitive ability (Witte et al., 2012). This is consistent with the warrior/worrier model posed by Goldman and colleagues (Goldman et al., 2005; Stein et al., 2006). This model postulates that the "warrior allele" (Val) leads to better stress resilience, whereas the "worrier allele" (Met) may be related to an advantage in memory and attention tasks. Consequently, Val allele or Met allele loading may be beneficial or disadvantageous depending on the circumstances. For example, one study revealed that Met homozygotes performed worse than Val homozygotes in a working memory task after a psychosocial stress induction (Buckert et al., 2012). Regarding studies assessing the role of *COMT* variation in stress reactivity in real life, three ESM studies found that psychosis patients that were homozygous for the Met allele showed more psychotic and/or affective reactivity to stress than Val carriers (van Winkel et al., 2008b; Collip et al., 2011, Peerbooms et al., 2012), whereas one study found that Val-Val individuals experienced greater paranoid reactivity than Met carriers in a general population sample (Simons et al., 2009). In addition, differential effects of *COMT* Val158Met genotype have also been found in the context of childhood adversity. Whereas one study revealed that the severity of positive and negative psychotic symptoms was greater for individuals homozygous for the Met allele with exposure to specific childhood adversity subtypes (Green et al., 2014), another one found a borderline significant interaction effect indicating that Val-Val individuals with childhood trauma exposure were more likely to endorse psychotic-like experiences (PLEs) in a nonclinical sample (Ramsay et al., 2013). However, there are no studies examining the interaction between *COMT* variation and childhood trauma in predicting stress-reactivity in real-life.

The relevance of psychosocial adversity in psychosis and its increasing conceptualization as a disorder of adaptation to social context (van Os et al., 2010) have raised interest in the interplay of biological systems that are critical to social behavior and which may interact with traditional psychobiological candidates in psychosis risk research. Some studies have recently focused on the importance of the interconnections between oxytocinergic and dopaminergic systems in social human behavior (e.g. Sauer et al., 2013). Crucially, the converging evidence of the interaction between oxytocin and dopamine within the mesocorticolimbic system has led to suggest that their interplay may regulate the salience (i.e., the attentional and motivational relevance) assigned to, specifically, *social* stimuli (Shamay-Tsoory and Abu-Akel, 2016). During the last decade, a growing literature has revealed that the neuropeptide oxytocin and its receptor (OTXR) modulate a large number of human social functions, including affiliative behavior, social competencies, and the propensity to use social interactions to manage stress (Feldman et al., 2016). In light of these findings, the *OXTR* 53576 polymorphism, which comprises a guanine (G) to adenine (A) substitution in the third intron of the OXTR gene (located on chromosome 3p25), has attracted substantial attention. The G allele of the *OXTR* 53576 has been associated with greater emotional support seeking under conditions of distress (in participants for whom support seeking is culturally normative; Kim et al., 2010) and with an increased benefit from social support in the context of a psychosocial laboratory stressor (Chen et al., 2011). Research has also shown that GG homozygotes display more sensitive parenting behavior (Bakermans-Kranenburg and van Ijendoorn, 2008) and greater dispositional and behavioral empathy (Rodrigues et al., 2009). Therefore, it has been suggested that GG individuals are more sensitive to the physiological effects of oxytocin in comparison with A carriers (Lucas-Thompson and Holman, 2013). In contrast, recent GxE studies have pointed to a detrimental role of the G allele in the context of childhood trauma (Tabak et al., 2013; Dannlowski et al., 2016). Overall, these findings seem to indicate that

individuals carrying the G allele may be more sensitive or responsive to the social environment (Lucas-Thompson and Holman, 2013). Only a few studies have investigated the role of *OXTR* rs53576 in psychosis. One study revealed a significant association between the A allele and the negative symptom of emotional withdrawal in a clinical sample (Haram et al., 2015), whereas another study found that patients with schizophrenia carrying the G allele had higher general psychopathology than patients with the AA genotype (Montag et al., 2013).

It is unknown whether the interplay between childhood trauma and *OXTR* (rs53576) plays a role in the expression of psychotic features or in heightening symptomatic and affective responses to social stress (i.e., stress reactivity). Similarly, there are no studies examining the combined action of *COMT* and *OXTR* polymorphisms on symptomatic and affective reactivity in real life. Therefore, the present study sought to investigate the interplay between childhood trauma, *COMT* and *OXTR* genetic variation on daily life experiences and momentary social stress reactivity in a nonclinical sample of young adults. Given that stress reactivity is a dynamic phenomenon and the importance of capturing social appraisals in the moment in their natural milieu, ESM provides the ideal framework for studying social stress reactivity. The aims were to examine whether the interaction of childhood trauma with *COMT* Val158Met polymorphism, *OXTR* rs53576 polymorphism, and the combined action of both markers in these genes: (1) is associated with levels of PLEs, paranoia, and negative affect, and (2) moderates psychotic-like, paranoid, and affective reactivity to social stress appraisals. We predicted that the interaction between childhood trauma and genetic variation would moderate social stress reactivity, such that the association of social stress appraisals with reality distortion experiences and negative affect would be stronger for Met carriers of the *COMT* with childhood trauma exposure and for G carriers of the *OXTR* rs53576 with childhood trauma exposure. Furthermore, taking into consideration the hypothesized

interaction of oxytocinergic and dopaminergic systems in the regulation of the salience of social cues (Shamay-Tsoory and Abu-Akel, 2016), we expected that individuals with childhood trauma exposure and a co-occurrence of Met and G alleles would show increased reactivity to social stress.

Methods

Participants

The sample forms part of PSYRIS-Barcelona, a longitudinal investigation examining psychosis risk and resilience. Participants were 206 nonclinically ascertained young adults from whom usable childhood trauma, ESM, and genetic (*COMT* and *OXTR* genotypes) data were obtained. The sample was drawn from a screening sample of 589 undergraduates at the Universitat Autònoma de Barcelona (Spain). Participants with high schizotypy scores were oversampled in order to ensure adequate representation of schizotypy in the present sample. A detailed description of the sample selection procedure has been provided in Barrantes-Vidal et al. (2013a, 2013b). The mean age of the sample was 21.3 years (*SD* = 2.4) and 78.6% were female.

Materials and procedure

Childhood trauma. The Childhood Trauma Questionnaire-Short Form (CTQ-SF) was used to assess experiences of trauma during childhood and adolescence. The CTQ-SF measures different forms of maltreatment (emotional, physical, and sexual abuse, and emotional and physical neglect) and the items are answered on a 5-point Likert-type scale ranging from "never true" to "very often true". In the present study, the overall childhood trauma score (i.e., the sum of items) was used for analyses.

ESM assessments. Personal digital assistants (PDAs) were used to collect ESM data. The PDAs signaled participants randomly 8 times daily (between 10 a.m. and 10 p.m.) for one week to complete short questionnaires. Participants had 5 minutes to initiate responding when they were signaled by the PDA. After this time interval or the completion of the questionnaire, the PDA shut down until the next signal. The full list of ESM items can be found in Barrantes-Vidal et al. (2013a). The ESM items used in the current study were answered on 7-point scales from "not at all" to "very much".

ESM measures of negative affect, PLEs, paranoia, and social stress appraisals were used for analyses. Specifically, following Barrantes-Vidal et al. (2013), we created indices of negative affect (4 items: feeling anxious, sad, angry, and guilty; alpha index =.80), PLEs (8 items: unusual senses, unusual thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and passivity; alpha index =.74) and paranoia (2 items: feeling suspicious and mistreated; alpha index =.70). Social stress during social contact was assessed with two items: "I feel close to this person (people)" (negative) and "Right now I would prefer to be alone" assessing appraisals of social interactions occurring in the moment. Note that the item "I feel close to this person (people)" is stated in positive terms, which allows to capture a spectrum of appraisals including both a positive and negative (i.e., stressful) valence.

Genotyping. DNA was obtained from buccal mucosa on a cotton swab using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain). The *COMT* Val158Met (rs4680) and *OXTR* rs53576 polymorphisms were genotyped using TaqMan 5' exonuclease assay (Applied Biosystems, AB). The probes for genotyping both SNPs were ordered through the TaqMan SNP genotyping assays AB assay-on-demand service. Polymerase chain reactions (PCR) were done

with a final volume of 5 µL, containing 5 ng of genomic DNA, 2.5 µL of TaqMan Master Mix and 0.25 µL of 20x genotyping assay (C_25746809_50) in the case of *COMT* and 0.125µL of 40x genotyping assay (C_3290335_10) in the case of *OXTR*. The cycling parameters were 95ºC for 10 minutes followed by 40 cycles of denaturation at 92ºC for 15 seconds and annealing/extension at 60ºC for 1 minute. PCR plates were read on an ABI PRISM 7900HT instrument and SDS v2.1. Software (AB) was used for the genotype analysis of data. Twenty percent individuals, chosen randomly, were re-genotyped to confirm the pattern reproducibility. Genotype distributions were in Hardy–Weinberg equilibrium (*COMT* Val-Val: 72, Val-Met: 95, Met-Met: 39; X^2= 0.59, df=1, *p*=0.44; *OXTR* AA: 19, GA: 93, GG: 94; X^2= 0.34, df=1, *p*=0.56).

Statistical method

The analyses focused on three different interactions between childhood trauma and genetic variation in relation to daily life experiences and momentary social stress reactivity. First, we analyzed the interplay between childhood trauma and *COMT* Val158Met; second, the interplay between childhood trauma and *OXTR* rs53576; and third, the interplay between childhood trauma and the combined action of *COMT* and *OXTR* genotypes in the prediction of daily life experiences. The combined action of *COMT* and *OXTR* genes was calculated by computing the number of Met and G alleles on *COMT* and *OXTR* genes, respectively. This method has been frequently used to assess complementary gene functions (e.g. Bondy et al., 2002; Clasen et al., 2011; Vrijsen et al., 2014). A score of 0 indicated no carriership of Met or G alleles on *COMT* and *OXTR* genotypes (i.e., participants were Val and A homozygotes on both polymorphisms); a score of 1 represented carriership of one Met allele or G allele on *COMT* and *OXTR* genotypes; a score of 2 indicated carriership of two Met - G alleles, a score of 3 represented carriership of three Met - G alleles, and a score of 4 indicated carriership of four Met - G alleles (i.e., participants were Met and G

homozygotes on both polymorphisms). The allele frequency distribution was as follows: 0 Met - G alleles: n=8 (3.9%); 1 Met - G allele: n=39 (18.9%); 2 Met - G alleles: n=78 (37.9%); 3 Met - G alleles: n=65 (31.5%); 4 Met - G alleles: n=16 (7.8%). Given that only eight participants were Val-Val and AA on both genes, we combined this group with that carrying one Met - G allele. Similarly, the small group carrying four Met - G alleles was combined with the group carrying three Met - G alleles. Therefore, the final frequency distribution of the three groups used in the analyses was as follows: 0-1 Met - G alleles: n=47 (22.8%); 2 Met - G alleles: n=78 (37.8%); 3-4 Met - G alleles: n=81 (39.3%).

ESM data have a hierarchical structure in which ESM ratings (level 1 data) are nested within participants (level 2 data). Therefore, multilevel or hierarchical linear modeling is the standard approach for the analysis of ESM data (Nezlek, 2011; Bolger and Laurenceau, 2013). The multilevel analyses examined two types of relationships between childhood trauma, genetic variation, and their interaction on daily life experiences. The first examined the independent direct effect of level 2 predictors (childhood trauma, genetic variation, and interaction term) on level 1 dependent measures (ESM ratings in daily life). The second type of analyses examined whether level 1 relationships (e.g., the association between social closeness and PLEs in daily life) varied as a function of level 2 variables (childhood trauma, genetic variation, and interaction term). In both analyses of direct effects and cross-level interactions, the effect of childhood trauma and genetic variation were examined separately (i.e., two separate models were used, one in which childhood trauma was the predictor and another in which genetic variation was the predictor). In order to examine the effect of the interaction between childhood trauma and genetic variation, the three variables (childhood trauma, genetic variation, and interaction term) were entered simultaneously in the same model. When a significant GxE was found, the effect of the interaction

was examined using simple slopes analyses. The multilevel and simple slopes analyses were computed with Mplus 6 (Muthén and Muthén, 1998-2010). Level 1 predictors were group mean centered and level 2 predictors were grand mean centered following Nezlek (2011). The data departed from normality in some cases, so parameter estimates were calculated using robust standard errors.

Results

Participants completed an average of 40.8 usable ESM questionnaires (*SD* = 9.1). There was no significant association of sex with childhood trauma (t=0.957, p=0.340), *COMT* Val158Met (X^2=5.61; p=0.061) or *OXTR* rs53576 genotype (X^2=3.31; p=0.191). The number of ESM usable records was also unassociated with these variables (childhood trauma: r=-0.11; p=0.13; *COMT* Val158Met: $F_{(2, 203)}$=0.446; p=0.641; *OXTR* rs53576: $F_{(2, 203)}$=0.563; p=0.560). In addition, the genotype variation did not significantly differ with respect to childhood trauma (*COMT* Val158Met: $F_{(2, 203)}$=0.558; p=0.573; OXTR rs53576: $F_{(2, 203)}$= 0.288; p=0.750).

Direct effects of childhood trauma, genetic variation, and their interaction

In line with our previous study examining separately abuse and neglect in this sample (Cristóbal-Narváez et al., 2016), total childhood trauma was associated with PLEs, paranoia, and negative affect (0.006, *SE* = 0.002, $p < 0.001$; 0.015, *SE* = 0.004, $p < 0.001$; 0.021, *SE* = 0.005, $p < 0.001$, respectively). It was also associated with the social stress appraisals, both with diminished social closeness (-0.033, *SE* = 0.007, $p < 0.001$) and with an increased preference to be alone (0.025, *SE* = 0.007, $p < 0.01$). In relation to genetic variation, the results showed that *COMT, OXTR,* and their combined action were not associated with PLEs, paranoia, or negative affect (see Supplemental Tables). The number of G alleles on *OXTR* gene was associated with increased

social closeness (0.198, *SE* = 0.095, p<0.05), but neither *COMT* nor the combined action of *COMT* and *OXTR* were associated with measures of social stress. Finally, the interaction of childhood trauma with *COMT, OXTR,* and their combined action was not associated with any of the daily life experiences.

Cross-level interactions with childhood trauma, genetic variation, and their interaction

Cross-level interaction analyses examined whether childhood trauma, genetic variation, and their interaction moderated the association of social stress appraisals with PLEs, paranoia, and negative affect in daily life (Tables 1-3). As described in a previous report of the PSYRIS-Barcelona study (Barrantes-Vidal et al., 2013a), appraisals of not feeling close to the person/people with whom the participant was at the time of the signal were associated with increased levels of PLEs, paranoia, and negative affect. Similarly, reports of preferring to be alone when with others were related to an increase of these experiences in the moment. Childhood trauma moderated these associations, such that they were significantly increased in individuals reporting high levels of childhood trauma. The *COMT* genotype did not moderate the associations of social stress with PLEs, paranoia or negative affect (Table 1), although there was a trend for the association between preference for being alone and PLEs to be moderated by *COMT* Met-alleles. The childhood trauma x *COMT* interaction moderated the association between preference to be alone and PLEs in the moment. Simple slopes analyses indicated that the association between preference for being alone and PLEs was significantly increased by exposure to childhood trauma in Met homozygotes participants (0.003, *SE* = 0.001, *t* = 2.75, *p* < 0.01), but not for those with the Val-Met or Val-Val genotypes (0.001, *SE* = 0.001, *t* = 1.56, ns; 0.000, *SE* = 0.001, *t* = 0.85, ns; see Figure 1).

The *OXTR* genotype did not moderate the associations of social stress with PLEs, paranoia or negative affect (Table 2). The childhood trauma x *OXTR* interaction moderated the association

of social closeness with negative affect, but not with PLEs or paranoia. Simple slopes analyses indicated that the association between diminished social closeness and negative affect was significantly increased by exposure to childhood trauma in GG participants (-0.005, *SE* = 0.001, *t* = -5.07, *p* < 0.001), but not in GA or AA participants (0.000, *SE* = 0.002, *t* = -0.19, ns; -0.002, *SE* = 0.003, *t* = -6.30, ns; Figure 2). Similarly, the childhood trauma x *OXTR* interaction moderated the association of preference to be alone with negative affect. Simple slopes analyses indicated that the association was significantly increased by exposure to childhood trauma in GG participants (0.005, *SE* = 0.002, *t* = 3.10, *p* < 0.01), but not in GA or AA participants (-0.003, *SE* = 0.003, *t* = -1.05, ns; -0.009, *SE* = 0.007, *t* = -1.26, ns). In addition, the childhood trauma - *OXTR* interaction moderated the association between preference for being alone and PLEs at a trend level. Simple slopes analyses indicated that the association was increased by exposure to childhood trauma in GG participants (0.002, SE = 0.001, t = 2.98, p < 0.01), but not in GA or AA participants (0.000, SE = 0.001, t = -0.28, ns; 0.001, SE = 0.002, t = 0.49, ns).

The combined action of the *COMT* and *OXTR* genes (i.e., number of Met - G alleles) did not moderate the associations of social stress with experiences in daily life (Table 3). The interaction of childhood trauma with the combined action of *COMT* and *OXTR* moderated the association of diminished social closeness with PLEs and negative affect, but not with paranoia. Simple slopes analyses indicated that, in both cases, the association was significantly increased by exposure to childhood trauma in the group carrying 3-4 Met - G alleles (PLEs: -0.002, *SE* = 0.001, *t* = -2.87, *p* < 0.01; negative affect: -0.006, *SE* = 0.001, *t* = -4.93, *p* < 0.001), but not in the groups carrying 0-1 or 2 Met - G alleles (PLEs: 0.000, *SE* = 0.001, *t* = -0.28, ns; -0.001, *SE* = 0.001, *t* = -1.11, ns; negative affect: -0.001, *SE* = 0.001, *t* = -0.60, ns; -0.003, *SE* = 0.002, *t* = -1.31, ns; Figure 3). Similarly, the childhood trauma x Met - G alleles interaction moderated the association of

preference for being alone with PLEs and negative affect. Simple slopes analyses showed that the associations were significantly increased by exposure to childhood trauma in the group carrying 3-4 Met - G alleles (PLEs: 0.002, *SE* = 0.001, *t* = 4.68, *p* < 0.001; negative affect: 0.005, *SE* = 0.002, *t* = 2.56, *p* < 0.05), but not for groups carrying 0-1 or 2 Met - G alleles (PLEs: 0.000, *SE* = 0.001, *t* = -0.31, ns; 0.001, *SE* = 0.001, *t* = 0.82, ns; Figure 4; negative affect: -0.005, *SE* = 0.003, *t* = -1.35, ns; 0.002, *SE* = 0.002, *t* = 0.70, ns).

Discussion

The present study extended previous GxE research by examining for the first time the role of a distal environmental exposure (childhood trauma), genetic variation in the *COMT* and *OXTR* genes, and proximal social stressors on the manifestation of negative affect and subclinical psychotic phenomena in real life. A critical feature of the study was that individuals' appraisals of social stress and their impact on symptomatic and affective reactivity were measured *in the moment*, allowing for a much more fine-grained and ecologically valid assessment of the complex person-environment interplay. The findings indicated that childhood trauma and genetic variation in the *COMT* and *OXTR* genes interact in shaping the expression of psychotic-like and affective reactivity to social stress in a nonclinical sample. These results highlight the relevance of examining the interplay between genetic and psychosocial environmental factors to enhance our understanding of the dynamic mechanisms implicated in the pathways to the extended psychosis phenotype.

Associations of childhood trauma, genetic variation, and their interaction with experiences in daily life

The results regarding the association of childhood trauma with psychotic-like, paranoid, and affective experiences were in line with our previous study in this sample (Cristóbal-Narváez et al., 2016). In that study we examined separately the effects of abuse and neglect from the CTQ and found that both adversity subtypes were associated with these daily life experiences. The findings support the accumulating evidence showing that interpersonal childhood trauma is a robust risk factor for positive psychotic phenomena (Varese et al., 2012; Velikonja et al., 2015). Regarding genetic variation, we found that *COMT* Val158Met, *OXTR* rs53576, and their combined action were neither directly associated with negative affect or reality distortion, nor moderated the association of childhood trauma with these experiences. Although research has yielded mixed results with the *COMT* genotype, the current findings are consistent with previous studies that also found no main effect of *COMT* on PLEs, heightening the relevance of the interaction with environmental factors (Savitz et al., 2010; Ramsay et al., 2013; Vinkers et al., 2013; Alemany et al., 2014). We are not aware of any previous studies examining the role of *OXTR* rs53576 polymorphism on psychosis proneness; nevertheless, our results are in line with the few studies conducted in psychosis populations, which found that *OXTR* rs53576 was not associated with the positive symptom dimension (Montag et al., 2013; Haram et al., 2015).

We also examined whether childhood trauma and genetic variation were associated with social stress appraisals in daily life. Childhood trauma was associated with a diminished perception of closeness during social interactions and a greater preference for being alone when being with people, suggesting that experiencing interpersonal stress in childhood may sensitize individuals to perceive greater interpersonal stress in adult life. This finding also appears to be in line with

evidence that parental maltreatment is linked to lower levels of self-reported social motivation and social support (Germine et al., 2015), and is consistent with prior research supporting the salient role of early interpersonal experiences in the dynamics of social interactions across development (e.g., Fonagy et al., 2014). We also found that the number of G alleles was associated with social closeness in daily life. This appears in line with previous studies that linked the G allele with prosocial features and displays of affiliative cues (Kogan et al., 2011). Although the mechanism by which genetic variation in *OXTR* impacts on these social functions remains unclear, it has been hypothesized that GG individuals have a more efficient receptor and thus a more robust oxytocin signaling, which may enable them to better draw on the beneficial effects of social-affiliative processes as compared with individuals with the A allele, which is associated with a less efficient oxytocinergic function (Feldman et al., 2016). The fact that *OXTR* was not associated with preference for being alone is consistent with this notion, as preference for being alone does not appear to directly tap affiliation, but rather, social discomfort or even simply having other motivational priorities at a particular moment. In other words, the content captured by appraisals of social closeness univocally refers to affiliative behavior, whereas the sources of variability for reporting a preference for being alone during social interactions are more heterogeneous and are not limited to individual differences in interpersonal affiliation.

Impact of gene-environment interactions on psychotic-like, paranoid, and affective reactivity to social stress appraisals

Regarding stress reactivity, we found that childhood trauma increased psychotic-like and paranoid reactivity to both social stress appraisals, as well as affective reactivity to diminished social closeness. These results concur with a few previous studies conducted in daily life supporting the notion that early and/or sustained exposure to interpersonal adversity sensitizes

(i.e., magnifies) the behavioral stress response to subsequent reexposures, even to minor stressful events (Glaser et al., 2006; Lardinois et al., 2011). The results indicated that genetic variation, either for *COMT* or *OXTR*, did not directly moderate stress reactivity in daily life. However, a trend was found for the number of Met alleles as a moderator of the association between preferring to be alone and PLEs. This resonates with ESM studies that reported that Met-homozygotes patients showed more psychotic and affective reactivity to event-related stress than those with the Val allele (van Winkel et al., 2008b; Collip et al., 2011). Furthermore, the interaction between childhood trauma and *COMT* moderated the association between preference for being alone and PLEs, indicating that psychotic-like reactivity to social stress was increased in Met homozygotes with childhood trauma exposure. This is in agreement with GxE studies showing that homozygosity for the Met allele and trauma exposure enhance the risk for posttraumatic stress disorder (e.g., Kolassa et al. 2010; Clark et al., 2013), and lend support to the warrior/worrier model (Goldman et al., 2005), which postulates that Met allele carriers ("worriers") tend to display more sensitivity to stress than Val carriers ("warriors"). Consistent with this model, imaging genetics studies have found that individuals with the Met allele, which is associated with higher dopamine levels (Lachman et al., 1996), display greater sensitivity to environmental aversive cues as indicated by elevated neuronal activity patterns in limbic brain structures (e.g. amygdala) and connected prefrontal areas (Smolka et al., 2005; Drabant et al., 2006).

Similarly, the interaction between *OXTR* rs53576 and childhood trauma moderated the associations of preference for being alone and diminished social closeness with negative affect. That is, individuals possessing a GG genotype and trauma exposure presented greater affective reactivity to both types of social stress appraisals. On the one hand, this finding is consistent with research showing that individuals carrying the G allele with high levels of childhood trauma

exhibited greater risk for depressive symptoms (McQuaid et al., 2013) and that G homozygotes exposed to multiple kinds of maltreatment were at greater risk for emotional dysregulation (Bradley et al., 2011). On the other hand, the mirror image of these results is that increases in closeness were associated with greater decreases in negative affect for GG participants with childhood trauma exposure, which suggests that experiencing closeness has a protective effect for these individuals. This seems to resonate with previous findings by Chen et al. (2011), who showed that OXTR variation influences the extent to which social support acts as a buffer against stress, with G carriers benefiting more from social support than AA carriers (in terms of lower cortisol levels and subjective stress responses). In addition, two studies have shown that GG individuals have higher amygdala responsiveness to emotional social cues than A carriers, and thus they may have enhanced social information processing (Tost et al., 2010; Dannlowski et al., 2016). Overall, our results support the view that GG participants may be more affected by and responsive to their social environments, as suggested by the social salience hypothesis of oxytocin and, importantly, seem consistent with the notion that the effects of oxytocin would not always be positive but rather context-dependent (Shamay-Tsoory and Abu-Akel, 2016).

New evidences of the combined action of COMT and OXTR genes

We found that the interaction of the number of Met - G alleles with childhood trauma moderated the association of social stress appraisals with PLEs and negative affect, pointing to an interplay between the HPA axis, dopaminergic and oxytonergic systems in response to social stress in daily life. The finding that the association of Met - G alleles with psychotic-like and negative affect reactivity only occurs in the context of exposure to childhood adversity is interesting in light of the notion that trauma may increase the risk for psychosis through a process of sensitization involving HPA axis dysregulation and converging on a common final pathway of dopamine

sensitization in mesolimbic regions (van Winkel et al., 2008a). Recent evidence has also indicated that genetic variation in OXTR appears to result in structural and functional alterations within limbic areas (e.g., the amygdala) depending on the presence of childhood trauma exposure (Dannlowski et al., 2016). Importantly, it has been suggested that due to the amygdala's crucial role in attention reorienting and the assignment of salience to social and affective stimuli, the amygdala may be the most likely region for the occurrence of the interactive effect of dopamine and oxytocin on these functions (Rosenfeld et al., 2011; Shamay-Tsoory and Abu-Akel, 2016). In this sense, one study revealed that the effect of central oxytocin secretion on amygdala response could be modulated by dopamine availability, suggesting an interaction between the oxytocin and dopamine systems in response to socially relevant stimuli (Sauer et al., 2013). Additionally, our findings suggest that social stimuli could be more salient for individuals with a higher number of Met - G alleles and with a history of interpersonal trauma, showing enhanced reactivity to *both* positive and negative proximal social exposures. Although these findings require replication before definitive conclusions can be drawn, this pattern of results appears to be in line with the differential susceptibility paradigm (Belsky and Pluess, 2009; 2013), which postulates that the same genetic variants could be associated with *risk* in adverse environments but may also be related to *resilience* in positive environments. Hence, individuals with a higher number of Met - G alleles and exposure to interpersonal trauma may be sensitized to experience more detrimental effects in response to proximal social stressors as well as more positive effects in response to close social interactions, which may serve as a buffer against psychopathological outcomes.

Conclusions, strengths and limitations, and future directions

To conclude, the present study sheds new light on how the interplay between genes involved in the dopaminergic and oxytocinergic systems and childhood trauma interact in the

prediction of psychotic-like and affective reactivity to social stress appraisals in real life. Although the study used ecologically valid measures that are considered to increase the power and reliability of GxE research (van Winkel et al., 2014; Myin-Germeys et al., 2009), some limitations need to be considered. The cross-sectional nature of the data limits causal interpretations regarding GxE interactions. Likewise, given that predictor and criterion ESM variables were assessed concurrently, causal inferences regarding the effects of social stressors cannot be made. Moreover, the use of a predominantly female university student sample in the present study did not allow for the examination of possible sex-differences of genetic variation in *COMT* and *OXTR* genes. On the other hand, the use of a nonclinical sample enhances the study of mechanistic processes by eliminating the confounding effect of the consequences of suffering a psychotic disorder, and provides evidence that the interplay of psychosocial adversity with *COMT* and *OXTR* genetic variation is relevant to understand individual differences in psychosis risk expression at the subclinical level. In fact, the finding of these associations in a non-clinically ascertained sample is especially striking and supports a continuum model of psychosis. Future studies should investigate whether this interplay is relevant for the expression of psychosis across general population, at-risk, and clinical samples. Furthermore, our results raise interest in further examining the seemingly differential-susceptibility pattern found for the moderating effects of the interaction of trauma with *OXTR* and with the combined effect of *OXTR* and *COMT* on the reactivity to appraisals of social interactions. In line with recent claims in differential-susceptibility research, this pattern of heightened sensitivity to both positive and negative environmental cues 'for better and for worse' should be formally tested with specific statistical tests (Roisman et al., 2012; Widaman et al., 2012).

Table 1. Cross-level interactions with childhood trauma, *COMT* Val158Met, and the childhood trauma - *COMT* Val158Met interaction (n=206)

Level 1 Criterion	Level 1 Predictor		Level 2 Predictors		
			Childhood trauma	*COMT*	Childhood trauma x *COMT*
	γ_{10} (*df*=204)		γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	Social closeness	-0.008 (SE=0.003)**	-0.001 (SE=0.000)*	-0.004 (SE=0.003)	-0.003 (SE=0.003)
Paranoia index	Social closeness	-0.026 (SE= 0.007)***	-0.003 (SE=0.001)*	0.000 (SE=0.008)	-0.001 (SE=0.009)
Negative affect index	Social closeness	-0.046 (SE=0.009)***	-0.003 (SE=0.001)**	-0.005 (SE=0.010)	-0.006 (SE=0.009)
Psychotic-like index	Prefer to be alone	0.019 (SE=0.004)***	0.001 (SE=0.001)*	0.012 (SE= 0.006)+	0.007 (SE=0.004)*
Paranoia index	Prefer to be alone	0.068 (SE= 0.010)***	0.003 (SE=0.002)*	-0.002 (SE=0.014)	-0.006 (SE=0.011)
Negative affect index	Prefer to be alone	0.125 (SE=0.014)***	0.002 (SE=0.002)	-0.005 (SE= 0.017)	0.004 (SE=0.010)

Trauma and *COMT* Val158Met were examined independently. The interaction was examined with trauma and *COMT* in the model.

+p<.07 *p <.05, **p <.01, ***p < .001.

Table 2. Cross-level interactions with childhood trauma, *OXTR* rs53576, and the childhood trauma - *OXTR* rs53576 interaction (n=206)

Level 1 Criterion	Level 1 Predictor[a]		Level 2 Predictors		
			Childhood trauma	*OXTR*	Childhood trauma x *OXTR*
	γ_{10} (*df*=204)		γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	Social closeness	-0.008 (SE=0.003)**	-0.001 (SE=0.000)*	0.001 (SE=0.004)	-0.004 (SE=0.003)
Paranoia index	Social closeness	-0.026 (SE= 0.007)***	-0.003 (SE=0.001)*	-0.009 (SE=0.011)	0.007 (SE=0.008)
Negative affect index	Social closeness	-0.046 (SE=0.009)***	-0.003 (SE=0.001)**	-0.008 (SE=0.011)	-0.014 (SE= 0.007)*
Psychotic-like index	Prefer to be alone	0.019 (SE=0.004)***	0.001 (SE=0.001)*	0.005 (SE=0.006)	0.008 (SE=0.004)+
Paranoia index	Prefer to be alone	0.068 (SE= 0.010)***	0.003 (SE=0.002)*	0.021 (SE=0.016)	0.011 (SE=0.013)
Negative affect index	Prefer to be alone	0.125 (SE=0.014)***	0.002 (SE=0.002)	0.004 (SE=0.021)	0.039 (SE=0.014)**

Trauma and *OXTR* rs53576 were examined independently. The interaction was examined with trauma and *OXTR* in the model.

+p<.07 *p <.05, **p <.01, ***p < .001.

Table 3. Cross-level interactions with childhood trauma, *COMT* Val158Met and *OXTR* rs53576, and the childhood trauma - *COMT* Val158Met and *OXTR* rs53576 interaction (n=206)

Level 1 Criterion	Level 1 Predictor[a]		Level 2 Predictors		
			Childhood trauma	*COMT* and *OXTR*	Childhood trauma x *COMT* and *OXTR*
	γ_{10} (*df*=204)		γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	Social closeness	-0.008 (SE=0.003)**	-0.001 (SE=0.000)*	-0.002 (SE=0.003)	-0.005 (SE=0.002)*
Paranoia index	Social closeness	-0.026 (SE= 0.007)***	-0.003 (SE=0.001)*	-0.004 (SE=0.010)	0.003 (SE=0.011)
Negative affect index	Social closeness	-0.046 (SE=0.009)***	-0.003 (SE=0.001)**	-0.011 (SE=0.009)	-0.016 (SE= 0.006)**
Psychotic-like index	Prefer to be alone	0.019 (SE=0.004)***	0.001 (SE=0.001)*	0.009 (SE=0.005)	0.009 (SE=0.003)*
Paranoia index	Prefer to be alone	0.068 (SE= 0.010)***	0.003 (SE=0.002)*	0.004 (SE=0.014)	0.007 (SE=0.012)
Negative affect index	Prefer to be alone	0.125 (SE=0.014)***	0.002 (SE=0.002)	-0.004 (SE=0.017)	0.030 (SE=0.012)*

Trauma and *COMT* Val158Met-*OXTR* rs53576 were examined independently. The interaction was examined with trauma and *COMT*-*OXTR* in the model.

*p <.05, **p <.01, ***p < .001.

Figure 1. Association between preference for being alone and PLEs across levels of childhood trauma in Val-Val, Val-Met and Met-Met participants.

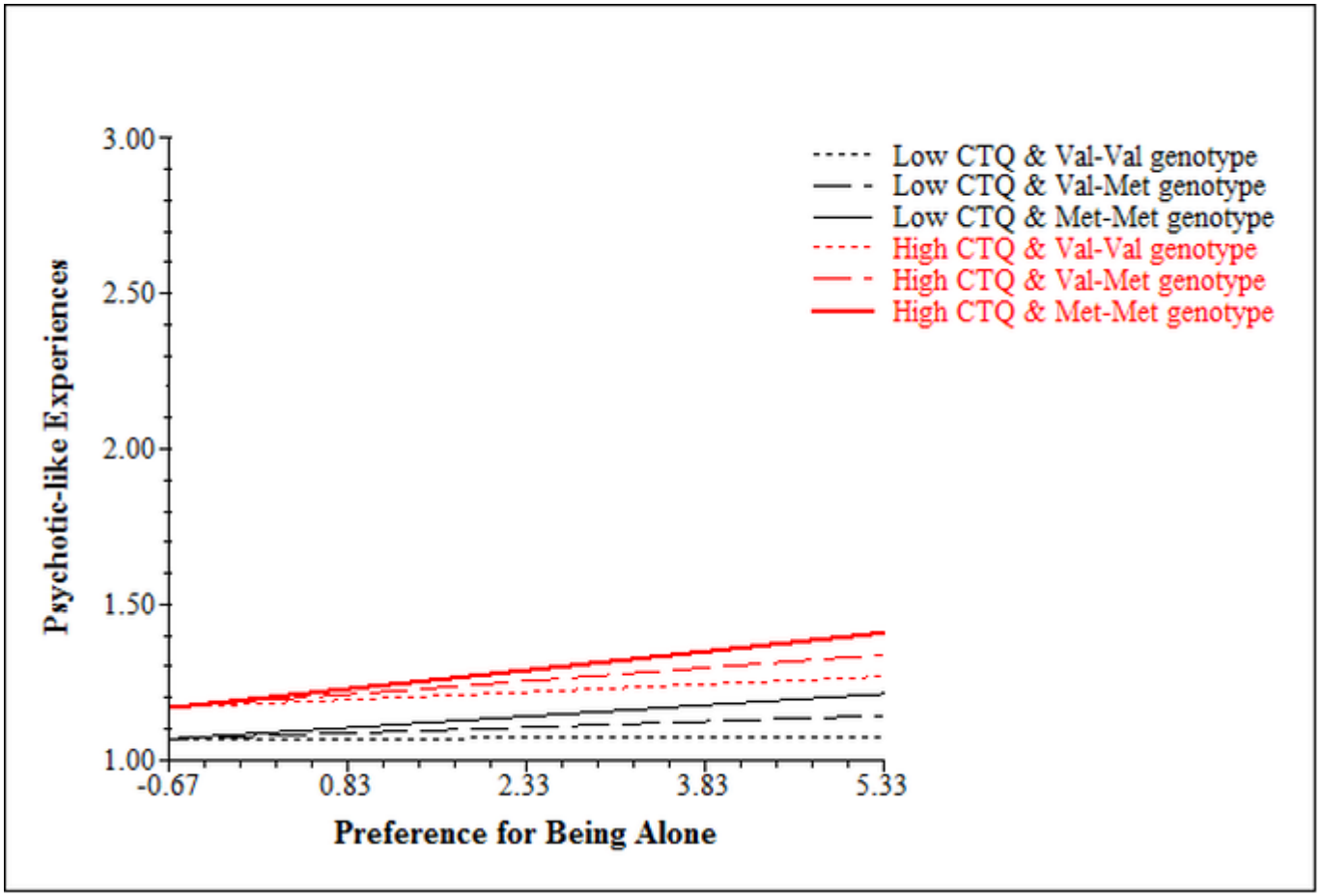


Figure 2. Association between social closeness and negative affect across levels of childhood trauma in GG, GA and AA participants.

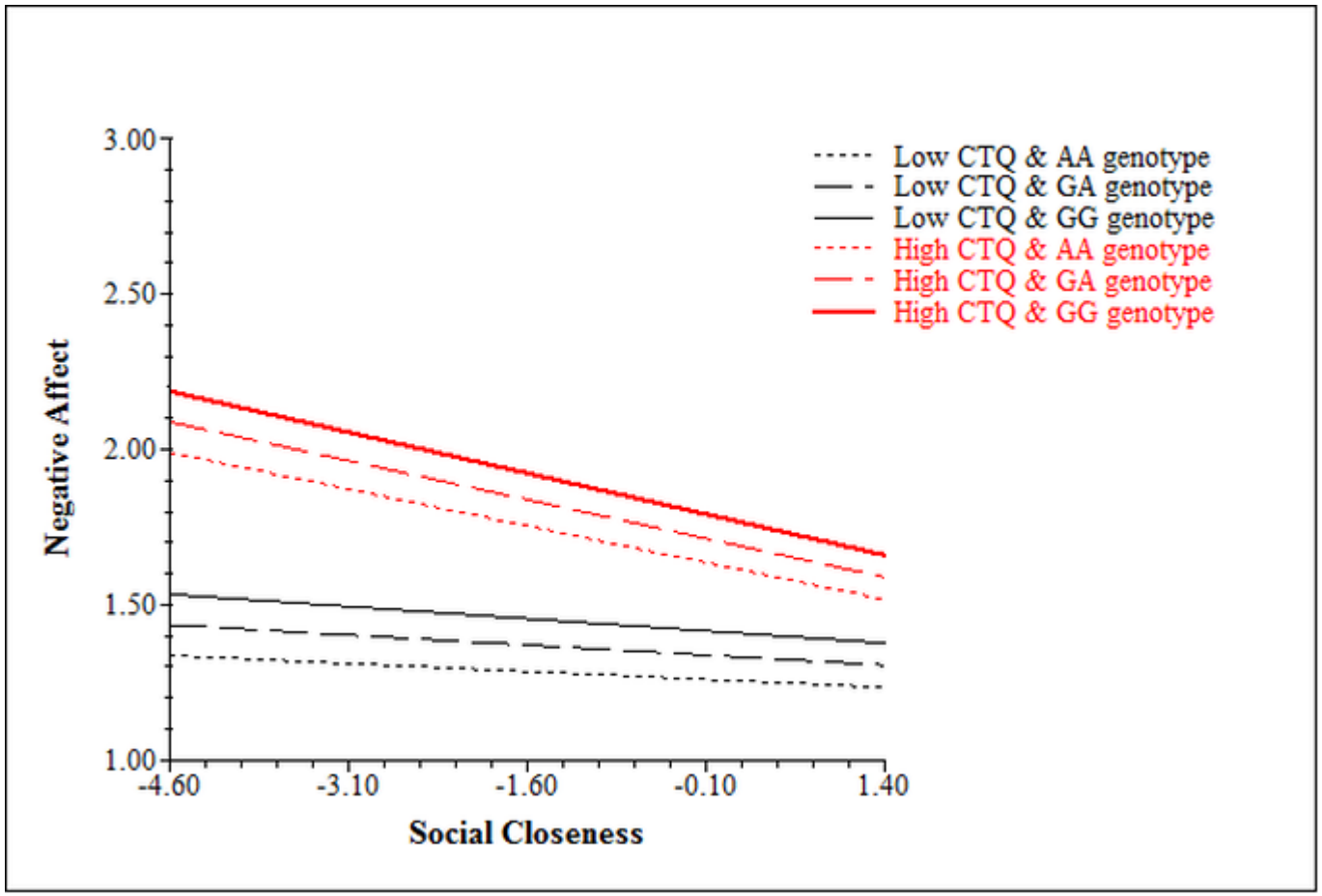


Figure 3. Association between social closeness and negative affect across levels of childhood trauma in 0-1, 2, 3-4 Met and G alleles of *COMT* Val158Met and *OXTR* rs53576.

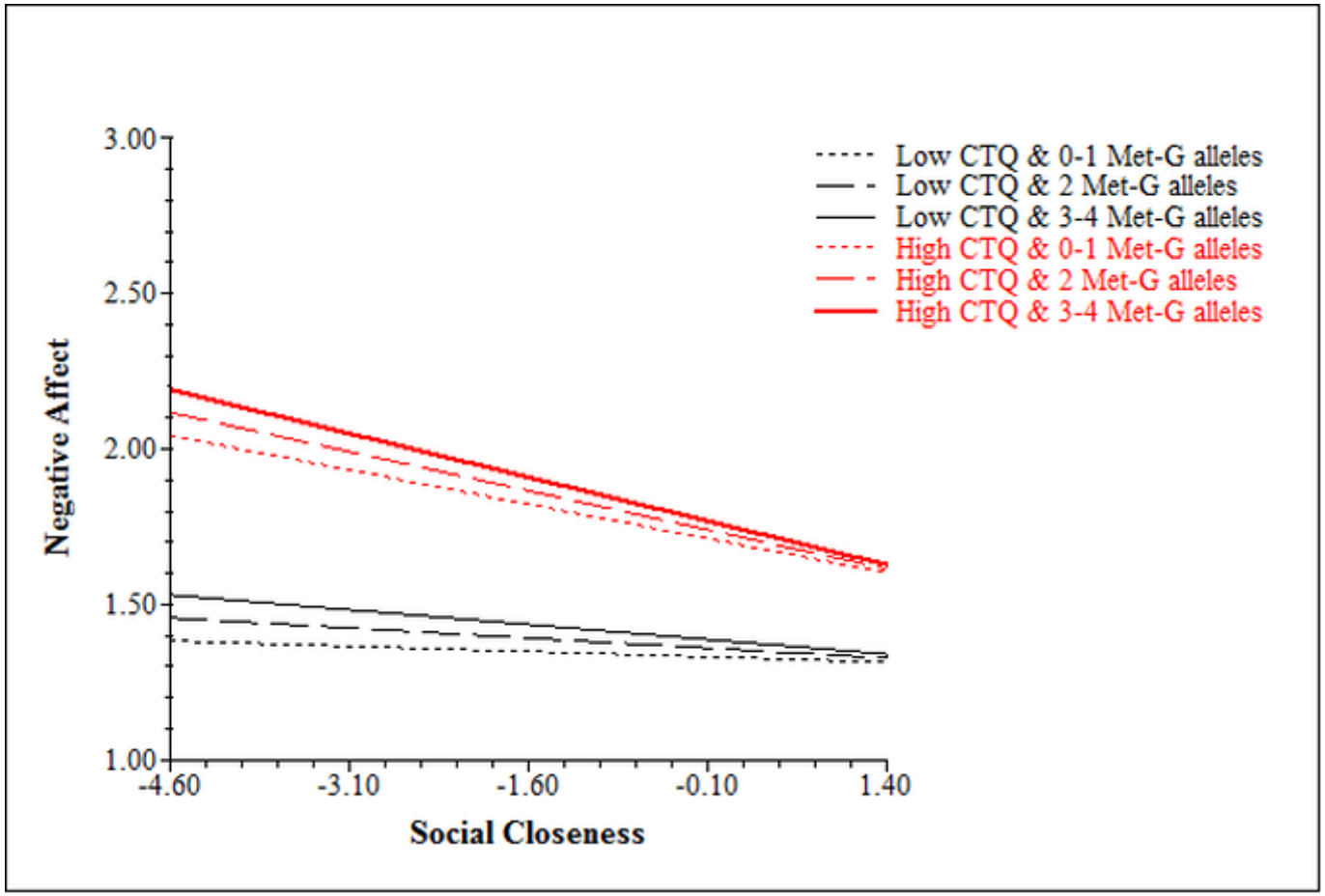
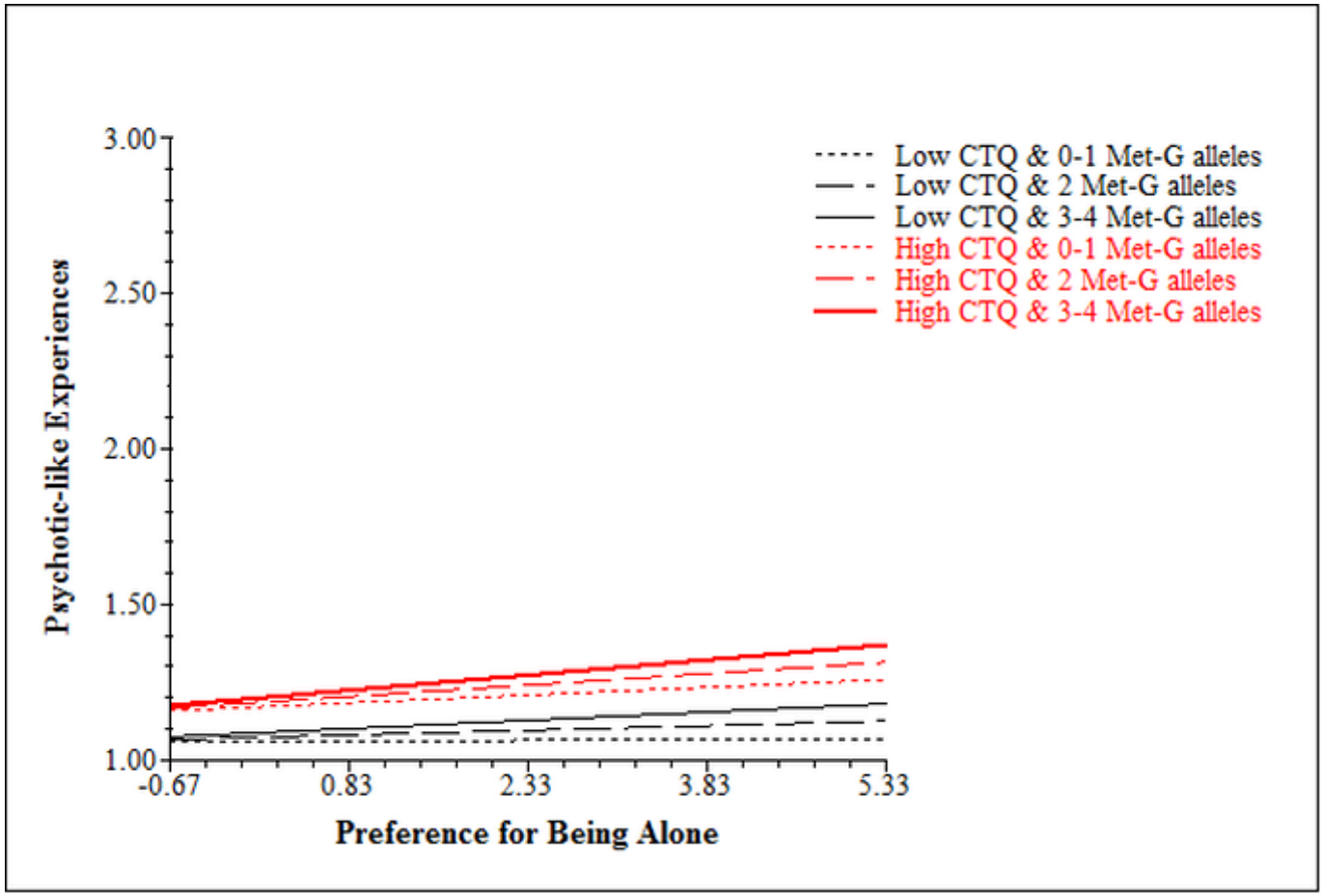


Figure 4. Association between preference for being alone and PLEs across levels of childhood trauma in 0-1, 2, 3-4 Met and G alleles of *COMT* Val158Met and *OXTR* rs53576.



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Supplementary material

Table S1. Main effects of childhood trauma, *COMT* Val158Met, and their interaction on psychosis spectrum experiences, negative affect and social stress appraisals (n=206)

Level 1 Criterion	**Level 2 Predictors**		
	Childhood trauma	*COMT*	Childhood trauma x *COMT*
	γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	0.006 (SE=0.002)***	0.001 (SE=0.017)	0.000 (SE=0.014)
Paranoia index	0.015 (SE=0.004)***	-0.021 (SE=0.030)	0.022 (SE=0.034)
Negative affect index	0.021 (SE=0.005)***	-0.009 (SE=0.047)	-0.022 (SE=0.035)
Social closeness	-0.033 (SE=0.007)***	-0.010 (SE=0.072)	-0.019 (SE 0.063)
Preference for being alone	0.025 (SE=0.007)**	-0.007 (SE=0.062)	0.029 (SE=0.052)

Trauma and *COMT* Val158Met were examined independently. The interaction was examined with trauma and *COMT* in the model.

*p <.05, **p <.01, ***p < .001

Table S2. Main effects of childhood trauma, *OXTR* rs53576, and their interaction on psychosis spectrum experiences, negative affect and social stress appraisals (n=206)

Level 1 Criterion	**Level 2 Predictors**		
	Childhood trauma	*OXTR*	Childhood trauma x *OXTR*
	γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	0.006 (SE=0.002)***	0.010 (SE=0.017)	0.004 (SE=0.012)
Paranoia index	0.015 (SE=0.004)***	0.012 (SE=0.034)	-0.014 (SE=0.026)
Negative affect index	0.021 (SE=0.005)***	0.070 (SE=0.048)	-0.007 (SE=0.030)
Social closeness	-0.033 (SE=0.007)***	0.198 (SE=0.095)*	-0.004 (SE 0.070)
Preference for being alone	0.025 (SE=0.007)**	0.004 (SE=0.012)	0.017 (SE=0.063)

Trauma and *OXTR* rs53576 were examined independently. The interaction was examined with trauma and *OXTR* in the model.

*p <.05, **p <.01, ***p < .001

Table S3. Main effects of childhood trauma, *COMT* Val158Met and *OXTR* rs53576, and their interaction on psychosis spectrum experiences, negative affect and social stress appraisals (n=206)

Level 1 Criterion	**Level 2 Predictors**		
	Childhood trauma	*COMT* and *OXTR*	Childhood trauma x *COMT* and *OXTR*
	γ_{01} (*df*=204)	γ_{01} (*df*=204)	γ_{03} (*df*=202)
Psychotic-like index	0.006 (SE=0.002)***	0.005 (SE=0.013)	0.003 (SE=0.014)
Paranoia index	0.015 (SE=0.004)***	-0.006 (SE=0.024)	0.008 (SE=0.032)
Negative affect index	0.021 (SE=0.005)***	0.026 (SE=0.035)	-0.021 (SE=0.036)
Social closeness	-0.033 (SE=0.007)***	0.111 (SE=0.081)	-0.035 (SE 0.065)
Preference for being alone	0.025 (SE=0.007)**	-0.022 (SE=0.065)	0.030 (SE=0.053)

Trauma and COMT Val158Met-OXTR rs53576 were examined independently. The interaction was examined with trauma and COMT-OXTR in the model.
*p <.05, **p <.01, ***p < .001

SECTION 4

GENE-ENVIRONMENT INTERACTION "FOR WORSE OR BETTER":

THE IMPACT OF EXPANDING OUR MEASUREMENT OF ENVIRONMENTAL FACTORS INCLUDING POSITIVE AND NEGATIVE EXPERIENCES

Chapter 5:

From Negative to Positive Experiences in Psychosis Expression:

The Interaction of Momentary Experiences and *FKBP5* Haplotype across the Extended Psychosis Phenotype

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Abstract

The present study examined with ecological validity whether the *FKPB5* haplotype moderates the association of positive and negative momentary appraisals with psychotic-like symptoms, paranoia, and negative affect in real-life in nonclinical and early-psychosis groups. Multilevel analyses indicated that, unlike the risk haplotype, the protective *FKBP5* haplotype moderated all the associations of positive appraisals with diminished psychotic-like symptoms, paranoia, and negative affect in daily life in early-psychosis individuals compared to nonclinical individuals. Results support the importance of investigating the "bright side" of gene-environment interactions in order to identify potential protective mechanisms in the extended psychosis phenotype.

Keywords: FKBP5 haplotype, gene-environment interaction, positive experiences, negative experiences, ecological validity, psychosis

Introduction

Extensive evidence indicates that the psychosis phenotype is expressed across a dynamic continuum that ranges from nonclinical (e.g., schizotypy, psychotic-like experiences) to clinical manifestations (Claridge, 1997; Kwapil & Barrantes-Vidal, 2015; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). In recent years, it has been highlighted that investigating continuities as well as discontinuities between clinical and nonclinical expressions may help to elucidate the heterogeneity in pathways to psychosis and in the identification of protective factors (Barrantes-Vidal, Grant, & Kwapil, 2013). In this regard, the study of patterns of gene-environment interactions (GxE) in clinical and nonclinical populations may contribute to our understanding of common and differential mechanisms operating across the psychosis continuum.

Recent GxE studies have indicated that the interaction of genetic risk variants on FK506 binding protein 5 (*FKBP5*) gene with psychosocial stressors is associated with psychotic experiences in clinical and nonclinical samples (Ajnakina et al., 2014; Alemany et al., 2016; Collip et al., 2013, Cristóbal-Narváez et al., 2016a, 2016b). Compelling evidence has suggested that individual variation in the *FKBP5* gene is linked to the dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, which has been identified as a critical neurobiological mechanism underlying the emergence of psychotic symptoms (van Winkel, Stefanis & Myin-Germeys, 2008). In particular, the minor risk alleles (C, A, T, T) of at least 4 *FKBP5* single nucleotide polymorphisms (SNPs; rs3800373, rs9296158, rs1360870, and rs9470080), as compared with non-risk or protective alleles (A, G, C, C), have been associated with a decreased sensitivity of the glucocorticoid receptor (GR) to circulating cortisol, entailing a diminished negative feedback regulation of the HPA axis that results in an abnormal prolongation of the stress response (Binder, 2009). Importantly, it has been shown that the rs1360780 SNPs included in the functional haplotype confer differential

effects in *FKBP5* mRNA and protein levels mediated by a differential chromatin conformation, resulting in different transcriptional effects between risk and protective alleles (Klengel et al., 2013).

So far research has focused on studying the effect of the interplay of *FKBP5* variation with adverse environmental exposures on psychotic phenomena, guided by the lens of the diathesis-stress model and disregarding the interaction of genetic variation with positive, and thus putative protective, environmental factors. Recently, however, it has been increasingly pointed out that individuals may differ in their susceptibility to the environment across a range of exposures (not just negative ones) and, therefore, that modulation by genetic variation should also be expected in relation to the benefit individuals may obtain from positive experiences (Pluess & Belsky, 2015). In light of this, new frameworks under which to consider GxE interactions have been developed. For example, the differential susceptibility model (Belsky & Pluess, 2009) highlights that individuals traditionally considered to carry greater vulnerability may be better conceptualized as being more plastic or malleable to the environment (for worse and for better). It suggests that the same genetic variants involved in increasing the negative effects of adverse experiences could also be involved in enhancing the likelihood of benefiting from positive ones. Another relevant model of GxE interactions is vantage sensitivity (Pluess & Belsky, 2013), which poses that certain genetic variants may enhance the likelihood of benefiting from positive exposures (without this also implying an increase in the susceptibility to negative exposures) — that is, vantage sensitivity is more than the "bright side" of environmental sensitivity as covered in differential susceptibility models (Pluess, 2015). Although these approaches have been scarcely considered within the psychosis field, the pertinence of incorporating the assessment of positive environmental experiences is underscored by GxE investigations in other stress-related phenotypes (e.g., Pluess & Belsky, 2013).

Another relevant issue that has received increasing attention in the context of GxE research has been the refinement of environmental measures (Moffit, Caspi, & Rutter, 2005). In this regard, the enhancement of precision and reliability offered by the use of ambulatory assessment strategies (such as the experience sampling method; ESM) should be helpful for examining genetic moderation of the effects of both positive and negative micro-level experiences. To our knowledge, there are no ESM studies investigating the potential moderation of individual variation involved in the regulation of the stress system, such as *FKBP5* variants, in the association of positive and negative momentary experiences with the psychosis phenotype. Importantly, there is a lack of studies with ecological validity that examine plausible genetic and environmental differences between nonclinical and clinical individuals, which should allow to identify risk and resilience targets for prophylactic interventions.

Therefore, the present study used ESM to elucidate whether the interplay of *FKBP5* variability with both positive and negative exposures impacts on the expression of psychotic and paranoid experiences, as well as negative affect, in the realm of daily life across the extended psychosis phenotype. Specifically, we examined whether the interaction of positive and negative appraisals with the *FKBP5* haplotype on symptoms and negative affect differed between early-psychosis and nonclinical groups. We predicted that the association of both positive and negative momentary appraisals with symptoms and negative affect would be greater in an early-psychosis group than in a nonclinical group, and that these associations would be moderated by *FKBP5* variability.

Methods

2.1. Participants

Data were collected as part of an ongoing longitudinal investigation examining psychosis risk and resilience (PSYRIS-Barcelona). The present study included a total of 319 participants reflecting different levels of expression of the psychosis phenotype for which ESM and genetic data were available (please see details in Cristóbal-Narváez et al., 2016b). The nonclinical group (which was oversampled for high schizotypy scores from a large nonselected group to contain significant variance in psychosis liability) consisted of 233 participants (mean age = 20.0 years, S.D. = 2.9 years; 25.3 % males), whereas the early-psychosis group included 86 patients (55 at-risk mental states for psychosis [ARMS] and 31 first episode psychosis [FEP]; mean age = 22.3 years, S.D. = 4.7 years; 69.8 % males). Ethical approval was obtained from the University Ethics committee and participants provided written informed consent.

2.2. Measures

Participants received personal digital assistants that signaled them randomly eight times daily for one week to complete brief assessments of positive and negative momentary experiences and symptoms on 7-point scales ranging from 1 (not at all) to 7 (very much). A detailed description of the ESM assessment can be found in Barrantes-Vidal, Chun, Myin-Germeys, & Kwapil (2013). The positive and negative experience items used in the present study focused on two domains in daily life: situational and interpersonal. The negatively valenced items were: “My current situation is stressful” and (when alone) “I am alone because people do not want to be with me”. The positively valenced items were: “My current situation is positive” and “Right now I feel that others care about me”. Three ESM indices were created and used as outcome measures: i) psychotic-like symptoms was

computed by averaging the scores for 8 items: unusual senses, unusual thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and passivity (coefficient $\alpha = 0.94$); ii) paranoia was the mean of two items: feeling suspicious and mistreated (coefficient $\alpha = 0.80$); iii) negative affect was the mean of four items: feeling anxious, sad, angry and guilty; (coefficient $\alpha = 0.89$).

2.3. Genotyping

Genomic DNA was extracted from saliva samples and genotyping was conducted using Applied Biosystems (AB) Taqman technology. Hardy–Weinberg equilibrium was verified in both samples (all $p < 0.05$). Analyses were conducted with the putatively functional haplotype derived from 4 *FKBP5* SNPs (rs3800373, rs9296158, rs1360780, and rs9470080). Participants were classified into three groups for analyses: (i) carriers of at least one protective haplotype (AGCC/-, n=157), (ii) carriers of one risk haplotype and one protective haplotype (AGCC/CATT, n=118), and (iii) carriers of at least one risk haplotype (CATT/-, n=44).

2.4. Statistical Analyses

ESM data have a hierarchical structure in which ESM ratings (level 1 data) are nested within participants (level 2 data). Linear mixed models were used to control for within-subject clustering of multiple observations using the "xtmixed" command in Stata 12 (StataCorp, 2011). Graphs were generated with the R program (www.r-project.org).

Two types of multilevel analyses were conducted in the present study. First, in order to examine whether the effect of the *FKBP5* haplotype on symptoms and negative affect differed between nonclinical and early-psychosis groups, we assessed the main effects of level 2 predictors (*FKBP5*, group, and FKBP5 x group) on level 1 outcome variables

(psychotic-like symptoms, paranoia, and negative affect) Second, to examine whether the moderating role of the *FKBP5* haplotype in the association of momentary appraisals with daily life outcomes differed between nonclinical and early-psychosis groups, cross-level interactions were conducted. Cross-level interactions tested whether level 1 relations (i.e., the association of positive and negative appraisals with symptoms and negative affect) varied as a function of level 2 variables (*FKBP5*, group, *FKBP5* x group). Finally, when an interaction was significant, the effect of the interaction was examined in each haplotype group using simple slopes analyses.

Results

Results indicated that the *FKBP5* haplotype was not associated with momentary symptoms or negative affect (psychotic-like symptoms: 0.026, *SE* = 0.036, ns; paranoia: 0.011, *SE* = 0.047, ns; negative affect: -0.031, *SE*= 0.051). However, as expected, participants in the early-psychosis group experienced more psychotic-like symptoms, paranoia, and negative affect than individuals in the nonclinical group (psychotic-like symptoms: 0.447, *SE* = 0.058, $p < 0.001$; paranoia: 0.500, *SE* = 0.075, $p < 0.001$; negative affect: 0.425, *SE* = 0.081, $p < 0.001$). No interaction effects were found between the *FKBP5* haplotype and group on symptoms or negative affect in daily life (psychotic-like symptoms: 0.138, *SE* = 0.082, ns; paranoia: 0.090, *SE* = 0.106, ns; negative affect: 0.122, *SE* = 0.114, ns).

Cross-level interaction analyses examined whether the *FKBP5* haplotype, group status, and their interaction moderated the associations of positive and negative appraisals with symptoms and negative affect in daily life (Table 1). Overall, the negative appraisals (situational stress and being unwanted) were associated with increased psychotic-like symptoms, paranoia, and negative affect, whereas the positive appraisals (current situation

being positive and feeling cared for by others) were associated with decreased symptoms and negative affect.

Regarding moderation effects, the *FKBP5* haplotype did not moderate the associations of positive or negative appraisals with symptoms or negative affect. Group status moderated the associations of situational stress with symptoms and negative affect, such that the associations were greater in the early-psychosis group compared with the nonclinical group. It also moderated the associations of the two positive appraisals with psychotic-like and paranoid symptoms in the moment. That is, as positive appraisals increased, early-psychosis participants experienced greater decreases in symptoms than their nonclinical counterparts.

The *FKBP5* haplotype by group interaction moderated all the associations of positive, but not negative, appraisals with decreased symptoms and negative affect in daily life. Simple slope analyses indicated that, among protective haplotype carriers (i.e., AGCC/-), the positive appraisal of the situation was associated with decreased symptoms in the early-psychosis group compared with the nonclinical group (psychotic-like symptoms: -0.087, *SE* = 0.018, $p < 0.001$; paranoia: -0.147, *SE* = 0.036, $p < 0.001$; negative affect; -0.043, *SE* = 0.038, ns). In addition, among protective haplotype carriers, the positive appraisal of feeling cared for by others was associated with decreased psychotic-like and paranoid symptoms, as well as negative affect, in the early-psychosis group compared to the nonclinical group (psychotic-like symptoms: -0.096, *SE* = 0.017, $p < 0.001$; paranoia: -0.156, *SE* = 0.035, $p < 0.001$; negative affect; -0.066, *SE* = 0.033, $p < 0.050$). Furthermore, among one protective and one risk haplotype carriers (i.e., AGCC/CATT), perceiving the situation as positive was associated with diminished psychotic-like symptoms in early-psychosis in comparison to nonclinical participants (situation positive - psychotic-like symptoms: -0.040, *SE* = 0.020, $p < 0.050$; paranoia: -0.024, *SE* = 0.035, ns; negative affect: 0.002, *SE* = 0.040, ns; others care

about me - psychotic-like symptoms: -0.004, *SE* = 0.022, ns; paranoia: 0.015, *SE* = 0.033, ns; negative affect: 0.014, *SE* = 0.036, ns). Finally, among risk haplotype carriers (i.e., CATT/-), no group differences were found in the association of both positive appraisals with symptoms (situation positive – psychotic-like symptoms: -0.017, *SE* = 0.035, ns; paranoia: 0.002, *SE* = 0.087, ns; negative affect: 0.135, *SE* = 0.079, ns; others care about me – psychotic-like symptoms: -0.035, SE = 0.027, ns; paranoia: 0.040, *SE* = 0.071, ns; negative affect: 0.088, SE = 0.055, ns).

Discussion

The present study investigated whether the interplay between *FKBP5* variation and contextual factors is not limited to adverse experiences, but expands into the full spectrum of positive and negative appraisals of real-life contexts. The study raised a novel finding indicating that the interaction of *FKPB5* variation and positive appraisals is associated with diminished psychotic-like and paranoid symptoms, as well as negative affect, in early-psychosis compared to nonclinical individuals. Another relevant finding from the current study was that early-psychosis individuals in comparison to nonclinical participants reported greater psychotic-like and paranoid reactivity to negative, but also to positive, contextual appraisals in daily life. Notably, the early-psychosis group differed from the nonclinical group in terms of symptomatic reactivity to positive, but not negative, appraisals in the interpersonal domain, suggesting that positive interpersonal appraisals may act as a relevant coping mechanism for help-seeking individuals, ameliorating the intensity of symptom expression in the realm of daily life. This lends support to the use of momentary clinical interventions with ecologically valid tools (Myin-Germeys, Birchwood, & Kwapil, 2011). These interventions have been useful for assessing individual symptom patterns in the realm of daily life, as well as for pinpointing both risk and protective environmental factors, and thus, providing new opportunities for treatment.

Although to our knowledge there are no previous studies investigating whether the *FKBP5* haplotype moderates the associations of positive experiences with symptom expression in daily life, the findings seems to resonate with a recent study in the context of responsiveness to psychotherapy in PTSD (Wilker et al., 2014). The study examined whether improvement in PTSD symptoms after exposure-based therapy differed as a function of *FKBP5* (*rs1360780*) variability. They found that, although no genetic differences on symptoms emerged between baseline and 4-month follow-up, individuals homozygous for the protective *FKBP5* C-allele continued to show a reduction in symptoms in the 10-month follow-up, whereas this was not found for carriers of the risk T-allele (Wilket et al., 2014). According to Pluess (2015), these results suggest that the C-allele may enhance vantage sensitivity in the context of exposure-based therapy in this population. Given that in the present study the protective haplotype was associated with diminished symptoms in the context of positive experiences for early psychosis participants (but not increased symptoms in the context of negative ones), the findings would seem to be in line with a vantage sensitivity interpretation for early psychosis as compared to nonclinical individuals, although it should be noted that we did not employ specific statistical tests to formally investigate the pattern of GxE interactions (as recommended by Roisman et al., 2012).

The present study has a number of strengths, including the estimation of a haplotype that increases the power to detect genetic associations (Crawford & Nickerson, 2005) and the use of valid ecological measures that are considered to increase the power and reliability of GxE research (Myin-Germeys et al., 2009). As regards to limitations, these include the composition of the nonclinical sample, which was comprised by college and tech school students with a predominance of female participants, and the fact that causal inferences of the effects of momentary positive and negative appraisals cannot be definitively drawn, given that ESM predictor and criterion variables were measured concurrently.

Overall, the study provides evidence of individual differences in the interaction of genetic variation with proximal environmental factors in nonclinical and early-psychosis individuals. Future studies should further investigate with ecological validity the potential mechanisms involved in the interplay of positive momentary exposures with protective individual variation in relevant genes for the homeostasis of the HPA axis, which may result in an adaptive response to stress in the realm of daily life. Moreover, empirical evidence from research examining patterns of reactivity to the environment could encourage real-word targeted strategies based on the knowledge of individual differences in the reactivity from negative to positive factors in the field of psychosis. This is a critical issue, given that, despite intense efforts in the early intervention paradigm (McGorry, Nelson, Goldstone & Yung, 2010), there continues to be a great amount of therapeutic helplessness associated with psychosis risk outcomes.

Table 1. Moderation by FKBP5 haplotype, group and the FKBP5 x group interaction of the association between daily-life experiences and appraisals with symptom indices (n=319)

Level 1 Criterion	**Level 1 Predictor**[a]		**Level 2 Predictors**		
ESM Symptoms	ESM Momentary Appraisals		*FKBP5* haplotype	Group: Early-psychosis vs nonclinical	*FKBP5 haplotype x Group*[b]
	γ_{10} (*df*=317)		γ_{11} (*df*=317)	γ_{12} (*df*=317)	γ_{13} (*df*=317)
			Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Negative Appraisals					
Psychotic-like index	Situation stressful	0.042 (0.007)***	0.007 (0.007)	0.081 (0.011)***	0.013 (0.015)
Paranoia index	Situation stressful	0.079 (0.013)***	0.006 (0.013)	0.112 (0.021)***	-0.005 (0.029)
Negative affect index	Situation stressful	0.216 (0.015)***	0.004 (0.014)	0.065 (0.023)**	0.013 (0.033)
Psychotic-like index	Alone b/c not wanted	0.104 (0.032)**	0.016 (0.029)	0.041 (0.040)	-0.005 (0.059)
Paranoia index	Alone b/c not wanted	0.202 (0.065)**	-0.038 (0.061)	0.110 (0.082)	0.014 (0.122)
Negative affect index	Alone b/c not wanted	0.157 (0.050)**	0.084 (0.046)	0.001 (0.060)	0.025 (0.092)
Positive Appraisals					
Psychotic-like index	Positive situation	-0.059 (0.008)***	0.005 (0.008)	-0.058 (0.013)***	0.035 (0.018)*
Paranoia index	Positive situation	-0.118 (0.017)***	0.002 (0.016)	-0.075 (0.025)**	0.085 (0.035)*
Negative affect index	Positive situation	-0.277 (0.018)***	0.022 (0.017)	-0.000 (0.026)	0.075 (0.037)*
Psychotic-like index	Others care about me	-0.034 (0.008)***	0.003 (0.008)	-0.045 (0.013)***	0.040 (0.017)*
Paranoia index	Others care about me	-0.083 (0.016)***	0.003 (0.015)	-0.052 (0.024)*	0.112 (0.033)**
Negative affect index	Others care about me	-0.133 (0.015)***	0.010 (0.014)	-0.008 (0.023)	0.078 (0.032)*

*p <.050, **p <.010, ***p < .001. [a]The table reports the coefficient of the association of the level 1 predictor and criterion for the analyses of *FKBP5* and group variables entered simultaneously. [b]The effect of *FKBP5* x group interaction term was examined over and above the main effects.

Fig 1. Group differences between nonclinical and early psychosis groups in the interaction of positive appraisals about the situation with *FKBP5* haplotype on psychotic-like and paranoid symptoms.

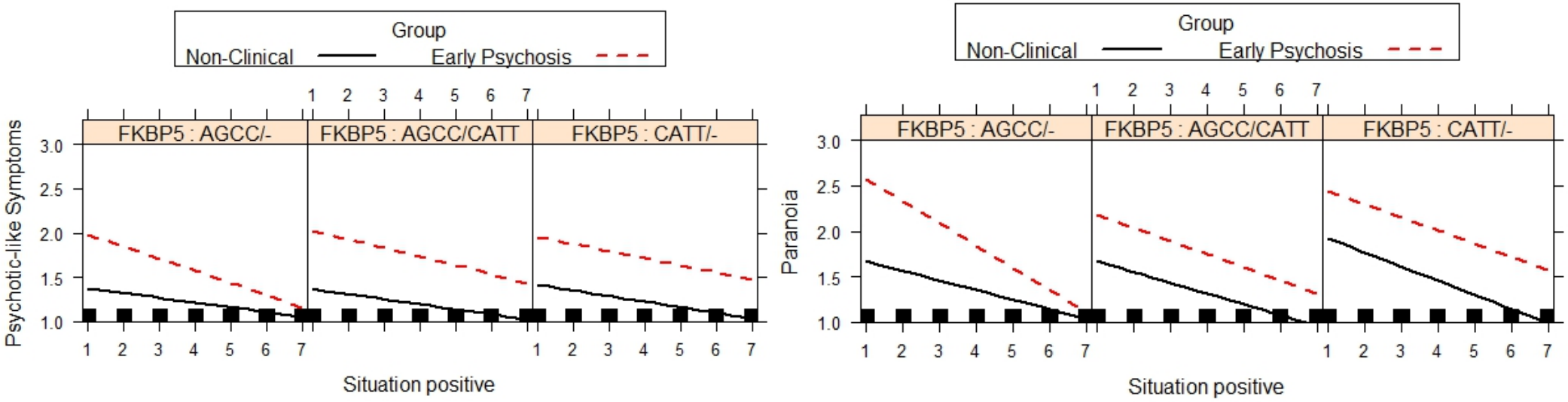
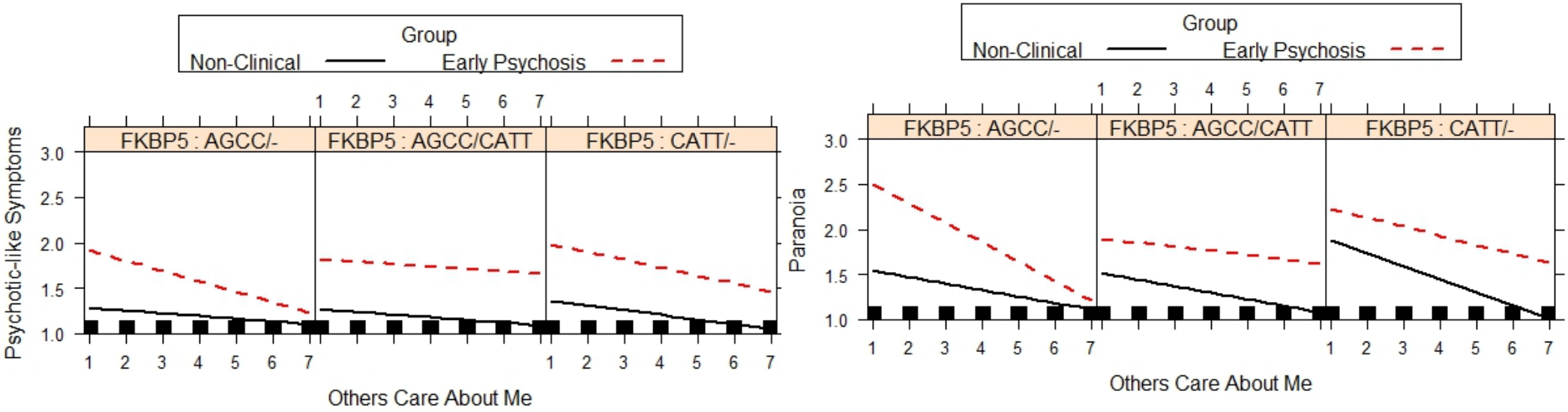


Fig 2. Group differences between nonclinical and early psychosis groups in the interaction of positive appraisals about others with *FKBP5* haplotype on psychotic-like and paranoid symptoms.



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5. GENERAL DISCUSSION

The main aim of this thesis was to examine the interplay between genetic and environmental factors on the expression of psychotic phenomena in the realm of daily life. In the process of working toward this aim, the first study sought to elucidate the mechanisms involved in the contribution of a range of childhood adversities in interaction with momentary stressors on the risk and expression of psychotic experiences in nonclinical young adults. Then, the role of SNPs relevant for key stress-regulation systems in interaction with distal and proximal environmental factors on psychotic features was investigated across the extended psychosis phenotype, that is, in both nonclinical and early-psychosis individuals. Thereafter the thesis provides novel contributions to gene-environment research by investigating further the interplay of relevant genetic variation with the combined action of both environmental factors. Finally, the thesis sheds new light on the plausible interplay between protective genetic and environmental factors against the development or amelioration of psychotic symptoms. The key results of the studies presented in each section of the thesis are summarized below, followed by a consideration of theoretical and clinical implications. Finally, the limitations of this thesis, the challenges in this field and directions for further research are also discussed.

5.1. Summary of Findings

Section one was dedicated to examining the synergy of distal and proximal environmental factors in the emergence of psychotic experiences in the realm of daily life. *Chapter 1* presented the association of childhood adversity subtypes with psychotic experiences (both psychotic-like and paranoid experiences) and negative affect, as well as their moderating role in affective and psychotic reactivity to situational and interpersonal forms of stress in nonclinical youth adults. As expected, interpersonal adversities involving

an intention to harm such as abuse, neglect and bullying were directly linked to the real-life expression of symptoms, whereas non-intentional adversities such as losses and general traumatic events were not related to any of the symptom domains. In addition, all childhood adversities investigated were associated with increased reactivity to some forms of stress in daily life. Importantly, only early-life *interpersonal adversities* were relevant to exacerbate psychotic and paranoid responses to *interpersonal stressors*. Collectively, findings support the notion that heightened stress reactivity is a critical mechanism involved in, specifically, the *positive* dimension of psychotic phenomena and add further evidence in favor of the hypothesis of a sensitization process related to early-life adversity in psychosis risk. Measurement-wise, self-report and interview measures were highly related and overall showed a pattern of concurrence in the profile of associations displayed with psychotic and paranoid experiences. Finally, it is worth noting that the study was conducted in a large nonclinical sample characterized by a wide distribution of schizotypy scores, that is, with large variation in terms of psychosis liability but free from the potential confounding factors associated with ill status (e.g., symptom severity, comorbidity, stigma, cognitive deterioration, medication side effects, etc.) that can be considered harmful in terms of, not only measurement reliability, but, critically, for the ability to unravel complex mechanistic processes implicated in symptom formation.

Section two was aimed at identifying relevant interactions between individual genetic variants, proximal and distal environmental factors across the extended psychosis phenotype. Specifically, *Chapter 2* presented a study in which the interplay of some of the most critical stress-regulation SNPs on *COMT, RGS4, BDNF, FKBP5 and OXTR* genes with both distal (self-report childhood trauma) and proximal (momentary real-life) stress was examined in nonclinical and early-psychosis individuals. The results indicated that, as expected, distal and momentary forms of stress have a relevant role in the expression of psychotic experiences in the total extended psychosis sample. It was also shown that the

interactions of *RGS4* and *FKBP5* risk haplotypes with distal, but not momentary stress, were associated with the expression of psychotic experiences. Moreover, when the early psychosis group and nonclinical groups were compared, results indicated that both environmental factors were more strongly associated with psychotic experiences in the early-psychosis group, pointing to the relevance of both factors in the expression of psychotic phenomena. Interestingly, *RGS4* and *FKBP5* risk haplotypes interacted with distal, but not proximal stress in the early-psychosis group, increasing the risk of daily-life psychotic experiences. Conversely, the risk allele of *OXTR* (rs2254298) increased psychotic reactivity to situational stress. This work provides a starting point for the identification of plausible relevant genetic variants that moderate the impact of distal and proximal environmental factors on psychosis, thus contributing to refine our understanding of how the complex interplay between genetic variants and environmental factors is involved in the real-world expression of psychotic features.

Section three presented two studies examining the joint contribution of both early-life and momentary environmental factors with genetic variation on psychotic phenomena. The work presented in *Chapter 3* described the interaction between interpersonal childhood trauma and *FKBP5* variability on psychotic experiences (psychotic-like and paranoid experiences) and negative affect as well as their moderating role in psychotic and negative affect reactivity to different forms of momentary stress in the flow of daily life. The results showed for the first time that the interaction of bullying with *FKBP5* variability was associated with psychotic-like and paranoid experiences and with negative affect in daily-life. It also moderated psychotic and affective reactivity to the social stress appraisal of feeling unwanted by others when being alone. The results underscored that the interplay between genetic risk, distal and proximal environmental factors has an impact on the expression of psychotic features. The findings therefore provided support to the 3-hit and

sensitization hypotheses (genes x distal x proximal environment) and lend further support to the increased relevance given to socially defeating appraisals in the real-world expression of psychotic experiences. *Chapter 4* described the interplay between interpersonal childhood trauma, *COMT* and *OXTR* genes on psychotic and negative reactivity to social stressors in real life. The study provided a novel contribution by showing that self-reported childhood trauma and individual variation in the *COMT* (rs4680) and *OXTR* (rs53576) genes interact in shaping the expression of psychotic-like and affective reactivity to social stress in daily life. Specifically, the results indicated that the interaction between childhood trauma and the number of *COMT* Met alleles moderated the association between a social stress appraisal (preference to be alone when in company) and psychotic-like experiences. The interaction of childhood trauma with the number of *OXTR* G alleles also moderated the associations of diminished social closeness during interactions and preference to be alone when in company with negative affect. More importantly, the interplay of childhood trauma with the combined action of *COMT* and *OXTR* variation (i.e., number of Met and G alleles) moderated the associations of both diminished social closeness and preference to be alone. This indicated that individuals with an elevated number of Met-G alleles and exposure to interpersonal trauma experienced more adverse effects in response to negative momentary stressors, but also more *positive* effects in response to *positive* exposures. This underscores the relevance of investigating the role of positive environmental factors as a possible buffer against psychopathology outcomes.

Section four was fully dedicated to examining the contribution of, not only negative, but also positive environmental factors. *Chapter 5* presented an examination of how the interplay between *FKBP5* variation and positive environmental factors interacts in ameliorating symptoms in the realm of daily life. The findings underscored the relevance of further investigating both "sides" of GxE interactions in the creation of a heightened

sensitivity to environmental influences, as it can actually have a protective role if positive factors are taken into account. This line of research can contribute to identify plausible protective mechanisms along the extended psychosis phenotype.

5.2. Integration of Findings and Theoretical Implications

The findings of this thesis contribute to a fast-growing body of evidence underscoring the importance of investigating with ecological validity the role of genetic variants, environmental factors and their interaction to unravel mechanistic pathways underlying symptom formation and risk expression across the extended psychosis phenotype. The results presented in *Chapter 2* indicated that both distal and proximal environmental factors impact in the real-world expression of psychotic features in early-psychosis and nonclinical individuals. The replicated associations of both stressors with psychotic experiences across the extended psychosis phenotype is consistent with previous epidemiological (e.g., Bentall & Fernyhough, 2008; Varese et al., 2012) and ESM research (e.g., Myin-Germeys & van Os, 2007) investigating early-life and momentary stress, respectively. Moreover, it lends further support to those etiological models (e.g. vulnerability-stress model) arguing that stress is a pivotal element involved in the manifestation of psychotic phenomena (e.g., Holtzman et al., 2013; Meehl, 1990; Zubin & Spring, 1977) and adds ecological validity to this longstanding clinical observation and theoretical model. Interestingly, it is also worth to note that consistent with previous studies (e.g., Trotman et al., 2014), the findings in *Chapter 2* further indicated that early-psychosis individuals, which represent allegedly a higher severity level in the hypothetical continuum of psychosis, reported greater levels of psychotic experiences as well as early and momentary adverse experiences than nonclinical subjects. Notably, the association between both risk factors and psychotic experiences was greater for help-seeking individuals than for psychosis-prone individuals. These findings also add further support to the validity of the ESM approach in psychosis research, and

contribute to show that early psychosis individuals are able to meaningfully inform about their internal experiences both in terms of symptoms and sophisticated psychological appraisals of both context and interpersonal interactions. On the other hand, consistent with the majority of previous candidate genes studies, none of the genetic variants were directly linked to daily life psychotic experiences (and main effects of genetic variants on symptoms were neither found in *Chapters 3-5*). However, it is worth noting that some interactions between genetic variants and environmental factors (both distal and proximal) on psychotic phenomena emerged in the early-psychosis group compared to the nonclinical group. In particular, *FKBP5 and RGS4* risk haplotypes interact with distal environmental factors whereas the A risk allele of *OXTR* (rs225498) interacts with proximal environmental factors in increasing levels of psychotic experiences in daily life. Taken together and, consistent with the psychosis continuum hypothesis, these findings suggest that although shared mechanisms (such as stress-sensitivity processes) are present across the extended psychosis phenotype in the realm life, there are also distinctive levels of severity between clinical and nonclinical individuals reflecting individual differences in risk and resilience factors, some of which may pave the way towards psychotic outcomes.

The link between different types of distal environmental factors and psychotic experiences, as well as the plausible moderating role of these factors in the association of proximal environmental factors with psychotic experiences was examined in detail whithin nonclinical participants in the study presented in *Chapter 1*. Consistent with recent studies (e.g., Arseneault et al., 2011; van Nierop et al., 2014), the findigs reveled that intentional maltreatment (either by commission or omission) and victimization perpetrated by same-age peers are directly meaningful in the expression of psychotic phenomena in the realm of life. Regarding the moderating role of adverse experiences in the association of proximal stressors with psychotic experiences, all the childhood adversities examined in *Chapter 1* -

including losses and traumatic events that were not directly related with psychotic experiences- were associated with psychotic reactivity in front of momentary stress, suggesting that early-life stress may sensitize individuals to react with increased psychotic responses to subsequent re-exposures of momentary stress in the realm of daily life. The findings in *Chapter 1* and, by extension results in *Chapter 3 and 4*, are thus in agreement with the sensitization hypothesis (Collip, Myin-Germeys, & van Os, 2008; van Winkel, Stefanis & Myin-Germeys, 2008) as well as with the general framework posited by the traumagenic neurodevelopmental model (Read, Fosse, Moskowitz, & Perry, 2014). Furthermore, the findings are consistent with the notion that stress reactivity is a relevant pathway for the experience of the reality distortion (Myin-Germeys & van Os, 2007).

Another relevant issue is the fact that unlike general traumatic events, which do not entail another human being as a key element inflicting harm, *interpersonal* childhood adversities – that is, abuse, neglect, bullying and losses – may be particularly relevant for psychotic and paranoid reactivity to daily life stressors of an *interpersonal* nature. In this line, findings in *Chapter* 3 and *Chapter 4* showed that bullying, abuse and neglect interact with individual variation on stress-regulation genes (*FKBP5, COMT, OXTR*) increasing psychotic reactivity to specific *interpersonal* stressors in nonclinical individuals. Therefore, taken together, the findings highlight that childhood adversities convey risk for psychotic outcomes depending on the complex interaction of genetic, person and environment factors across lifelong development (Debbané & Barrantes-Vidal, 2015).

More specifically, the findings in *Chapter 3* also indicated that the interaction of bullying with the *FKBP5* risk haplotype increased symptomatic reactivity to appraisals of feeling unwanted when alone (but not other forms of interpersonal stress appraisals). In this regard, it is interesting to note that the experience of being bullied and the appraisal of feeling unwanted could be considered as distal and momentary experiences of social defeat. These

findings therefore concur with the social defeat hypothesis (Selten, van der Ven, Rutten, & Cantor-Graae, 2013) by showing that socially defeating experiences, that is, exclusion and subordination, may be relevant in interaction with other factors to create an enduring liability to psychotic experiences. In this regard, the findigs indicated that distal and proximal experiencies of social defeat interact with individual genetic variation (*FKBP5* risk haplotype) involved in the regulation of HPA axis. This suggests that bullying experiences in childhood and their re-exposure in daily life may result in a sensitization of HPA axis, increasing the risk for psychotic symptoms in nonclinical individuals. Importantly, the interaction of *FKBP5* haplotype with social defeat experiences in daily life (without the presence of bullying) were not associated with any symptom domain, highlightening the relevant role of early-life experiences in the underlying stress sensitization processes involved in reality distorsion experiences. Similarly, the results reported in *Chapter 4* also indicated that the impact of *COMT (rs4680)* and *OXTR (53576*) SNPs in the psychotic and affective reactivity in real life, only occurs in the context of prior exposure to childhood interpersonal adversity (self-reported abuse and neglect). Collectively, the results suggest that *interpersonal* adversities may increase the risk for psychotic features through a process of biological sensitization involving HPA axis dysregulation and converging on a common final pathway of dopamine sensititzation in mesolimbic regions (van Winkel et al., 2008). Importantly, in these areas (e.g. amygdala), dopamine and oxytocin interconnections would be especially relevant for the salience of *interpersonal* stimulus (Shamay-Tsoory & Abu-Akel, 2016).

Another important consideration is that the results in *Chapter 4* also revealed that individuals with a higher number of risk alleles in both genes (*COMT and OXTR*) in interaction with early-life experiences present an increased reactivity to negative, but also, to *positive* social appraisals. These findings can be considered to be consistent with the

differential susceptibility paradigm (Belsky & Plues, 2009) and underscore the need to investigate further individual differences taking also into consideration positive environmental factors in the expression of psychotic experiences. In light of these previous findings, *Chapter 5* intended to elucidate in greater detail the role of positive environmental exposures in interaction with individual genetic variation in nonclinical and early-psychosis individuals. The results showed that *FKBP5* variation and positive environmental factors interact in ameliorating psychotic experiences in the realm of daily life in early-psychosis compared to nonclinical individuals. Importantly, findings shed new light on how the interplay between positive momentary experiences and protective individual variation in stress-regulation genes may act as a long-term buffer against the development of psychotic disorders.

Finally, it is worth mentioning that although the work of this thesis focused on stress sensitization and stress reactivity mechanisms, it is of course not suggested that these are the only relevant mechanisms necessary to account for the psychosis-stress link. For instance, and in line with studies in attachment research (e.g., Mikulincer & Shaver, 2007; Sheinbaum, Kwapil & Barrantes, 2014), results in *Chapter 1* suggested that *interpersonal* adversities may act in conjunction with early relational experiences in shaping negative internal models of the self and others that may be activated by specific *interpersonal* stressors, ultimately contributing to the experience of reality distorsion. In *Chapter 2*, it was suggested that according with previous studies (Feldman et al., 2016), attachment styles may also interact with genetic variation (e.g., *OXTR* rs225498) resulting in a greater risk for psychopatology. Furthermore, in *Chapter 2* and especially in *Chapter 3*, it was also suggested that according with recent molecular studies (Klengel & Binder, 2015), early-life stress in interaction with *FKBP5* risk alleles induce epigenetic changes that may result in individual differences in glucorticoid receptor sensitivity, resulting in a dysregulation of HPA axis. Therefore, a

plethora of other psychological (e.g., distortion of cognitive schemas, attachment styles) and biological (e.g., epigenetic) mechanisms are undoubtedly necessary to meaningfully apprehend the complex mechanistic pathways leading from adversity to psychosis risk and expression processes (the so called emerging field of "functional enviromics"; van Os, Rutten, & Poulton, 2008).

5.3. Implications for Clinical Work

The early psychosis detection and intervention paradigm developed over the last two decades has focused on the identification of people at risk for developing psychosis, preventing and ameliorating the onset and course of illness. This new framework moved the focus of clinical psychology and psychiatry from chronic to early stages of psychosis, which has significantly contributed to mapping the risk stage and the onset of psychosis disorders. However, we still lack a refined understanding of "micro-level" *processes* in early psychosis occurring where people do suffer their problems, that is, in daily-life. The description of theoretically and clinically meaningful psychological appraisals which trigger psychotic and affective reactivity reported in this thesis through ESM methodology seems to contribute to the necessary understanding of these processes in order to empirically base targets for therapeutic intervention.

On the other hand, although it is generally accepted that "the sooner treatment is begun, the better the outcome may be", some evidence has pointed out important concerns regarding early intervention strategies. A major issue is the adverse consequences of incorrectly identifying and treating people that are actually not at high risk to develop a disease, as well as the risks of applying even nonspecific treatments in early life stages. Thus, notwithstanding the substantial efforts performed and their undoubtful success in many dimensions, it is clear that some outstanding issues still need to be addressed. The findings

of the present thesis seek to contribute to these pending concerns with the intention of refining our current conceptualization and operationalization or "risk status" and achieving future promising interventions.

Given the complex etiology of psychotic phenomena and the multiple pathways that probably lead to similar phenotypic expressions, it seems obvious that early interventions should adapt to specific individual needs rather than use common strategies with the same purposes for all subjects (Haddock & Lewis, 2005). Thus, distinct groups of individuals may require different approaches within a broad spectrum of psychotherapeutic models. The findings of these studies attempted to contribute to the characterization of different risk pathways and mechanisms that should ultimately refine our capacity to deliver person-based treatments. Another important point relates to promoting safer intervention methods, such as psychoeducation and psychosocial programs rather the delivery of a traditional medication treatment by default. Ideally, these early-intervention strategies should be based on non-invasive therapeutic strategies, for instance, implementing the intervention at a precise moment in which is required. In this regard, the ecological momentary interventions (EMIs) using experience sampling methodology recently devised in the field of psychosis constitute a promising and an innovative assessment and intervention approach, allowing to tailor personalized interventions toward individual needs in the specific moment that are needed (Myin-Germeys, Klippel, Steinhart, & Reininghaus, 2016). An innovative approach would be the delivery of this real-world treatment, but targeted on specific clusters of early-psychosis individuals showing specific risk factors and mechanisms. In this line, a real-world intervention based on an accurate identification of individuals at risk (through both traditional and experiencing sampling methods enriched with information about stress-relevant genetic variants) and, their posterior division into different groups or clusters

according to critical shared mechanisms (e.g., high sensitivity to the environment), would result in new treatment opportunities for psychotic illness.

Another consideration is that the findings obtained in this thesis indicated that a relevant interaction between genetic, person and environment factors is involved in the increased risk for psychotic symptoms in the realm of daily life. In particular, the results of this thesis, in line with new evidence (e.g., Sommer et al., 2016), revealed that environmental and biological factors can modulate positively or negatively the trajectory towards the development of psychotic features. Future clinical work based on follow-up studies should further investigate these possible positive and negative trajectories in the real-world expression of psychotic experiences not only at one specific point in time, but over a period of time. The development of these trajectories over the time would provide a better explanation of the contribution of genetic and environmental factors (both risk and protective) across the extended psychosis phenotype. However, the recent etiological evidence that advocates for positive and negative effects of genetic and environment factors on the developmental trajectories of psychotic phenomena has not yet been embodied into preventive interventions. In this regard, it is imperative to devise new real-word targeted strategies based on the knowledge about the capacity of at risk and already psychotic persons of showing differential reactivity to negative and positive factors. This evidence seems to be especially relevant for the field of psychosis given that, despite the efforts and achievements of the early intervention paradigm, there continues to be a great amount of therapeutic helplessness associated with psychosis risk outcomes.

5.4. Limitations and Strengths

The studies presented in this thesis have notable strengths, but also a number of shortcomings which need to be considered. Overall, and to the best of our knowledge, the

work presented in these empirical studies combines a number of strengths not always present in this literature, such as a substantial sample size, the number of SNPs in various candidate genes, the simultaneous measurement of both distal adversity along with ecologically valid measures of momentary stress and symptoms, and the study of these all these factors at various levels of psychosis expression.

First, as previously mentioned, the use of ecologically valid data obtained prospectively and repeatedly during a one-week period (and its subsequent analysis using sophisticated statistical analyses) increases the feasibility and the reliability of the GxE approach. However, the cross-sectional nature of the data precludes conclusions about causal direction. Future reports from our research group on the PSYRIS-Barcelona longitudinal study will be able to describe GxE trajectories over time and disentangle the causal influences of the variables studied. Furthermore, other data analytic approaches employing time-lagged associations will help to draw more firm conclusions about the directionality of these associations. For instance, we have previously reported how stress levels reported at the previous assessment predicted the increase of psychotic-like experiences at the current level but not the other way around. Second, the adequate representation of schizotypy traits in the nonclinical sample enables a more appropriate comparison between clinical and nonclinical individuals. The nonclinical group is not composed of "supernormal" controls with scarce variability in terms of the behavioral expression of psychosis risk. Nevertheless, the nonclinical sample was constituted by college students and technical school students rather than general population participants and had a female predominance. Although there is no prior evidence of sex-differences in terms of GxE on the real-world expression of psychotic phenomena, future studies should also examine the potential impact of gender in samples with a more balanced distribution in terms of gender. Moreover, the early-psychosis sample was comprised of a combination of ARMS and FEP individuals given that 1) no a

priory hypotheses were offered regarding the possible effect of group (ARMS vs FEP) on the GxE analyses performed, and 2) this ensured sufficient statistical power for the complex analyses conducted. Third, childhood adversities were examined by means of self-report and interview methods in the first study. The results in this study showed no substantial differences between two methods, which lend reliability to the further examination of solely self-report data in the GxE studies. Nonetheless, although retrospective assessments of childhood adversities tend to be accurate due to use of these suitable and standardized procedures (Bifulco & Thomas, 2013), the existence of memory distortions in the responses of individuals, in particular in help-seeking participants, cannot be ruled out. Some evidence, though, seems to indicate that this concern may be somewhat overrated, as objective and subjective ratings of abuse seem to be highly convergent (e.g., Barrantes-Vidal, 2014). Fourth, the estimation of haplotypes was used with the aim of increasing our power to detect genetic associations (Crawford & Nickerson, 2005). However, due to limited number of SNPs available in both samples, it was not always possible to achieve this objective.

5.5. Challenges and future directions

There is an emerging approach claiming that information collected with ESM could be employed to understand indiviuals' symptom networks or the "psychopathology connectome" (van Os et al., 2008) which would not only provide a personalized map and clinical assessment but also greatly contribute to delineate personalized mechanistic pathways of symptom formation and maintenance as well as contextual factors inducing exacerbation or amelioration. Importantly, given that psychopathological symptoms are dynamic and may change within the same individual over time, momentary assessment techniques can also be used to examine the micro-structure of psychopathology. In this regard, recent studies have started to analyze the structure of psychopathology as an intricate network, which is characterized by the presence of mental states called "nodes" (i.e.,

psychotic symptoms or psychological strengths) that when activated, may generate other mental states (Borsboom & Cramer, 2013; Kendler, Zachar, & Craver, 2011). Further studies though this new network paradigm may offer novel opportunities to map transdiagnostic processes (Wigman et al., 2015).

Another relevant issue relates to the considerable progress made by GxE research in the last few years. Until recently, the hypothesis-based molecular genetic candidate approach has been the most favored method for the examination of gene-environment interactions (Munafò, Zammit & Flint, 2014). However, the inconsistencies across these studies as well as the difficulty in establishing a reliable comparison between them have led to the emergence of other approaches (Modinos et al., 2013). Fast-growing GWAS studies using novel sophisticated tools (e.g., polygenic risk scores) in large international samples have been able to identify thousands of millions of SNPs and, to provide methodology homogeneity in the field, which contrasts with the broad flexibility design of prior candidate genes approaches (e.g., different range or definition of the studied variables). However, despite of this improvement at technological level, the GWAS approach has even worse constraints than genetic candidate approach (e.g., lack of knowledge of the concrete nature of genetic risk variation and its biological meaning; Munafo et al., 2014).

Furthermore, open questions remain about which mechanisms may underlie the association of genetic profiles with environmental risk factors in increasing the risk for schizophrenia (Iyegbe, Campbell, Butler, Ajnakina, & Sham, 2014). In this line, it has been suggested an alternative approach that also allows for the screening of environmental factors, known as Genome-Environment-Wide Interaction Studies (GEWIS; Khoury & Wacholder, 2009). Althought it has not yet been widely used in schizopherenia research due to statistical penalties, the GEWIS approach offers a broader range of new opportunities, especially in conjunction with other approaches (Aschard et al., 2013). For instance, given that animal

models may be useful in revealing promising candidate GxE interactions, the examination of the biological impact of environmental variants in these models can allow more targeted and hypothesis-driven GEWIS inquiries (Modinos et al., 2013). Notably, animal models are helpful in detecting GxE interactions as well as in examining the dynamics of biological and environmental interactions. For example, animals carrying a hypothesized biological risk factor may be exposed to a wider range of putative risk environmental factors allowing for the examination of developmental, functional or structural negative outcomes, as well as the detection of the critical time period of these exposures over time. Thus, animal models may also inform the potential critical windows of exposure and relevant mechanisms in humans.

Thus far, many lines of research have indicated that agnostic molecular strategies and hypothesis-based candidate approach can work in tandem. Prior knowledge from candidate genes approaches has consistently indicated that social environmental stressors impact on genes implicated in specific mechanisms, for example, in dopamine sensitization (e.g., Howes & Kapur, 2009). Therefore, it seems evident that future challenges should lie in the integration of sophisticated novel techniques, which increase the statistical power needed to detect GxE interactions, with a theoretical and empirical rationale of the plausible mechanisms involved in the etiology of the schizophrenia and related disorders. This has shed light on the need to join forces among social and genetic research for the purpose of moving forward in the GxE area (Kirkbride, 2014). To this end, *The European Network of National Networks Studying Gene-Environment Interactions in Schizophrenia (EU-GEI)* has recently started to undertake the identification of polygenic risks scores in large-scale samples but taken into consideration the wide evidence of biological pathways underlying environmental risk (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions, 2014). In light of these promising challenges in the field, it seems evident that the days of the disputes between environment and genetic research are gone. A

new era of discoveries and breakthroughs based on the collaboration and the cooperation between social, psychological and genetic sciences has finally arrived to the GxE approach.

5.6. Conclusions

The studies presented in this thesis provide new insights on how the interplay between genetic and environmental (distal and proximal) factors impact on psychotic phenomena in the realm of daily life. Overall, the main conclusions of the present thesis are:

1) Intentional forms of childhood adversity (abuse, neglect and bullying), but not losses or general traumatic events, are associated with psychotic experiences in the realm of daily life. Unlike general traumatic events, adversities of an interpersonal nature (abuse, neglect, bullying and losses) exacerbate psychotic experiences in response to both situational and social stressors.

2) Both distal (childhood trauma) and proximal (momentary, real-life) psychosocial stressors are associated with the real-world expression of psychosis risk across the extended psychosis phenotype. Compared to nonclinical subjects, early-psychosis individuals show greater increases in psychotic experiences in response to both stressors. The risk haplotypes (*FKBP5, RGS4)* and the risk allele *OXTR* (rs2254298) interact with distal and proximal environmental factors, respectively, increasing the real-world expression of psychosis in early-psychosis individuals. An interaction of *COMT* and *BDNF* variants with distal or proximal stressors was not found.

3) Bullying interacts with the *FKBP5* risk haplotype in shaping the real-world expression of psychosis proneness and social stress reactivity. Similarly, the exposure to other distal interpersonal adversities (combination of self-reported abuse and neglect) with *COMT (rs4680)* and *OXTR (53576*) SNPs exacerbate psychotic and affective reactivity to social stressors.

4) Early-psychosis individuals reported greater psychotic reactivity to negative, but also to *positive* daily-life experiences. The interaction of the protective *FKBP5* haplotype and positive experiences results in the amelioration of daily-life psychotic experiences in in help-seeking individuals, but not in nonclinical participants.

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Universitat de Barcelona, Departament de Psiquiatria

PUBLICATIONS

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., Ballespí, S., de Castro-Catala, M., Peña, E., …Barrantes-Vidal, N. (2016). The Interaction between Childhood Bullying and the FKBP5 Gene on Psychotic-Like Experiences and Stress Reactivity in Real Life. *PLoS ONE 11*(7): e0158809. doi:10.1371/journal.pone.0158809

Cristóbal-Narváez, P., Sheinbaum, T., Ballespí, S., Mitjavila, M., Myin-Germeys, I., Kwapil, T.R., & Barrantes-Vidal, N. (2016). Impact of Adverse Childhood Experiences on Psychotic-Like Symptoms and Stress Reactivity in Daily Life in Nonclinical Young Adults. *PLoS ONE 11*(4): e0153557. doi:10.1371/journal.pone.01535

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., Ballespí, S., de Castro-Catala, M., Peña, E., …Barrantes-Vidal, N. (2016). Interplay between childhood trauma, *COMT* and

OXTR genes on psychotic-like reactivity in real life. Manuscript submitted for publication.

Cristóbal-Narváez, P., Sheinbaum, T., Myin-Germeys, I., Kwapil, T. R., Dominguez-Martínez, T., Racioppi, A., ...Barrantes, Vidal. N. (2016). *Do stress-regulation genes moderate the real world association of stress and psychotic experiences in early psychosis?.* Unpublished manuscript

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., Castro-Catala, M., Peña, E., Myin-Germeys, I., ...Barrantes-Vidal, N. (2016). *From Negative to Positive Experiences in Psychosis Expression: The Interaction of Momentary Experiences and FKBP5 Haplotype across the Extended Psychosis Phenotype.* Unpublished manuscript

de Castro-Catala, M., **Cristóbal-Narváez, P.**, Kwapil, T.R., Sheinbaum, T., Peña, E., Barrantes-Vidal, N., Rosa, A., (2016). Association between RGS4 variants and psychotic-like experiences in nonclinical individuals. *Eur. Arch. Psychiatry Clin. Neurosci.* doi:10.1007/s00406-016-0676-7

de Castro-Catala, M., van Nierop, M., Barrantes-Vidal, N., **Cristóbal-Narváez, P.**, Sheinbaum, T., Kwapil, T. R., …Rosa, A. (2016). Childhood trauma, BDNF Val66Met and subclinical psychotic experiences. Attempt at replication in two independent samples. *Journal of Psychiatric Research, 83*, 121-129

Domínguez-Martínez, T., **Cristóbal-Narváez, P.**, Barrantes-Vidal, N., Kwapil, T.R. (in press). Clinical and Psychosocial Characterization of Early Psychosis Patients from the Sant Pere Claver-Early Psychosis Program in Barcelona (Spain). *Actas Españolas de Psiquiatría.*

European Network of National Networks Studying Gene Environment Interactions in Schizophrenia (EU-GEI). (2014). Identifying gene–environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin*, *40*(4), 729–736

Portero-Tresserra M., **Cristóbal-Narváez P.**, Martí-Nicolovius M., Guillazo- Blanch G., Vale-Martínez A. (2013). D-cycloserine in prelimbic cortex reverses scopolamine-induced deficits in olfactory memory in rats. *PLoS ONE 8*(8): e70584. doi:10.1371/journal.pone.0070584

Vilagrà, R., Domínguez-Martínez, T., **Cristóbal-Narváez, P.**, Kwapil, T.R., & Barrantes-Vidal, N. Presentation of clinically and subjectively rated measures of psychotic phenomena in At-Risk Mental States (ARMS), First Episode of Psychosis (FEP) and non-clinical samples. Manuscript in preparation

Vilagrà, R., Domínguez-Martínez, T., **Cristóbal-Narváez, P.**, Kwapil, T.R., & Barrantes-Vidal, N. Correlates of subjective at-risk Basic Symptoms with clinically rated symptoms of psychosis in At Risk Mental States (ARMS), First Episode of Psychosis (FEP) and non-clinical samples. Manuscript in preparation

CONFERENCE PRESENTATIONS

2016

Barrantes-Vidal, N., **Cristóbal- Narváez, P.**, Sheinbaum, T., Monsonet, M., Hinojosa-Marqués, L., Domínguez-Martínez, T., Kwapil, T. R. (2016). *Childhood trauma is associated with psychotic-like symptoms and stress reactivity in daily life in individuals with an at-risk mental state for psychosis*. Presented at the 2016 meeting of the 5th Schizophrenia International Research Conference, Florence, Italy.

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., Mitjavila, M., de Castro-Catala, M., Peña, E., Kwapil, T. R., Barrantes-Vidal, N. (2016). *The interaction between bullying and FKBP5 haplotype on psychotic-like experiences and reactivity to stress: Does it matter in real life?*. 5th Schizophrenia International Research Conference, Florence, Italy. April 2nd-6th. Poster Presentation

Hinojosa-Marqués, L., Sheinbaum, T., **Cristóbal-Narváez, P.**, Monsonet, M., Kwapil, T. R., Domínguez-Martínez, T., Barrantes-Vidal, N. (2016). *Early psychosis patients' and relatives' attachment style: Association with clinical and functional presentation*. 5th Schizophrenia International Research Conference, Florence, Italy. April 2nd-6th. Poster Presentation

Monsonet, M., **Cristóbal-Narváez, P.**, Sheinbaum, T., Domínguez-Martínez, T., Kwapil, T. R., Barrantes-Vidal, N. (2016). *Paranoia and facets of self-esteem in early psychosis: Associations across psychometric and real-life assessment methods.* 5th Schizophrenia International Research Conference, Florence, Italy. April 2nd-6th. Poster Presentation

Sheinbaum, T., **Cristóbal-Narváez, P.**, Ballespí, S., Mitjavila, M., Myin-Germeys, I., Kwapil, T. R., Barrantes-Vidal, N. (2016). *Impact of adverse childhood experiences on psychotic-like symptoms and stress reactivity in daily life in nonclinical young adults*. 5th Schizophrenia International Research Conference, Florence, Italy. April 2nd-6th. Poster Presentation

2015

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., Ballespí, S., Mitjavila, M., de Castro-Català, M., Kwapil, T.R., Barrantes-Vidal, N. (2015). *Adverse Childhood Experiences, COMT and BDNF genes: An examination of gene-environment interplay on Psychosis*

Proneness. 5th European Conference on Schizophrenia Research, Berlin, Germany. September 24-26th. Poster Presentation.

Cristóbal-Narváez, P., Sheinbaum, T., Rosa, A., de Castro-Català, M., Kwapil, T. R., & Barrantes-Vidal, N. (2015). *The relation of momentary appraisals and BDNF variability with psychotic-like and paranoid symptoms in daily life: An experience sampling study*. Poster presentation at the International Convention of Psychological Science. Amsterdam, The Netherlands. March 12-14th. Poster Presentation.

de Castro-Catala, M., Peña, E., Sheinbaum, T., **Cristóbal-Narváez,** P., Kwapil, T.R., Barrantes-Vidal, N. & Rosa, A. (2015). *The FKBP5 and its modulating role on the psychosis-inducing effects of childhood trauma: new evidences from GxE studies*. 5th European Conference on Schizophrenia Research, Berlin, Germany. September 24-26th. Poster Presentation.

Hinojosa-Marqués, L., Sheinbaum, T., **Cristóbal-Narváez, P**., Racioppi, A., Monsonet, M., Kwapil, T.R., Domínguez-Martínez, T., Barrantes-Vidal, N. (2015). *Association of early psychosis patients' and relatives' attachment style with clinical and functional presentation*. 5th European Conference on Schizophrenia Research, Berlin, Germany. September 24-26th. Poster Presentation.

Monsonet, M., **Cristóbal-Narváez, P.,** Sheinbaum, T., Domínguez-Martínez, T., Kwapil, T.R., Barrantes-Vidal, N. (2015). *Association of different measures and facets of self-esteem with paranoia in early psychosis*. 5th European Conference on Schizophrenia Research, Berlin, Germany. September 24-26th. Poster Presentation.

Peña, E., de Castro-Catala, M., Kwapil, T.R., Sheinbaum, T., **Cristóbal-Narváez, P.,** Barrantes-Vidal, N. & Rosa, A. (2015). *Moderating effect of the candidate gene p250GAP in the association between childhood trauma and psychosis liability*. 5th

European Conference on Schizophrenia Research, Berlin, Germany September 24-26th. Poster Presentation.

2014

Cristóbal- Narváez, P., Rosa, A., de Castro-Català, M., Sheinbaum, T., Kwapil, T. R., & Barrantes-Vidal, N. (2014). *COMT moderation of the association between momentary stress and psychotic-like experiences in daily life*. 4th Schizophrenia International Research Conference, Florence, Italy. April 5-9th. Poster Presentation.

Domínguez-Martínez, T., **Cristobal, P.**, Sheinbaum, T., Kwapil, T. R., & Barrantes-Vidal, N. (2014). *Gender differences in the effect of childhood trauma experiences on prodromal symptoms and personality disorder traits in young adults at high-risk for psychosis*. 4th Schizophrenia International Research Conference, Florence, Italy. April 5-9th. Poster Presentation.

de Castro-Catala, M., Barrantes-Vidal, N., Kwapil, T.R., **Cristóbal-Narváez, P.**, & Rosa, A. (2014). *Relationship between the BDNF Val66Met polymorphism, Childhood Trauma and Psychosis-proneness*. 4th Schizophrenia International Research Conference, Florence, Italy. April 5-9th. Poster Presentation.

de Castro-Catala, M., Barrantes-Vidal, N., Pena, E., Kwapil, T.R., **Cristóbal- Narváez, P.**, & Rosa, A. (2014). *Impact of the schizophrenia candidate gene RGS4 on psychosis-proneness*. 4th Schizophrenia International Research Conference, Florence, Italy. April 5-9th. Poster Presentation.

Rosa, A., Pena, E., de Castro-Catala, M., Kwapil, T.R., **Cristóbal-Narváez, P.**, & Barrantes-Vidal, N. (2014). *p250GAP a new candidate gene for schizophrenia and psychosis-proneness?*. 4th Schizophrenia International Research Conference, Florence, Italy. April 5-9th. Poster Presentation.

2013

Cristóbal-Narváez, P., Rosa, A., de Castro-Català, M., Sheinbaum, T., Kwapil, T.R., Barrantes-Vidal, N. (2013). *COMT Moderation of the Association between Momentary Stress and Psychotic-Like Experiences in Daily Life*. Lemanic International Exploratory Workshop on Schizotypy, Geneva, Switzerland. December 5-7th. Poster Presentation.

2012

Cristóbal-Narváez P., Portero-Tresserra M., Martí-Nicolovius M., Guillazo-Blanch G., Vale-Martínez A. (2012). *D-cycloserine in prelimbic cortex reverses scopolamine-induced memory deficits in a social transmission of food preferences task*. 8th Federation of European Neuroscience Societies - Forum of Neuroscience, Barcelona, Spain. July 14-18th. Poster Presentation.

PARTICIPATION IN RESEARCH PROJECTS

2012-2013

Project title: **The Interaction between Daily-Life Stressors and Subjective Appraisals of Psychotic-Like Symptoms in the Psychosis Prodrome during One Year Follow-up: Ecological and Dynamic Evaluation with the Experience Sampling Methodology and Analysis of Gene-Environment (Stress) Interactions.**

Funding body: Fundació La Marató de TV3

Rating agency: Agencia d'Avaluació de Tecnologies Mèdiques de la Generalitat de Cataluña

Principal investigator: Neus Barrantes-Vidal

2012 - 2015

Project title: **Factors and their Interactions Underlying Symptom Formation and Outcome across the Nonclinical and Clinical Continuum of Psychosis**

Principal Investigator: Neus Barrantes-Vidal

Funding Agency: Spanish Ministry of Economy and Competitiveness (MINECO), Plan Nacional de I+D+I (National Plan of R+D)

Project Reference: PSI2011-30321-C02-00

Duration: January 2012 to December 2015 (3 years + 1 year extension)

Subproject 1: A Study of the Psychological (Person) Factors Mediating the Impact of Environmental Adversity on Psychosis Risk and Outcome

Principal investigator: Neus Barrantes-Vidal

Project Reference: PSI2011-30321-C02-01

Amount Funded: 165.770€

Subproject 2: Genetic Variability in Emotion Regulation, Social Bonding and Hypothesised Candidate Pathophysiological Mechanisms in Psychosis: Relationship with Daily-Life Stress-Sensitivity and Expression of the Psychosis Continuum Phenotype

Principal Investigator: Araceli Rosa de la Cruz

Project Reference: PSI2011-30321-C02-02

2014-2016

Project title: **Consolidated Research Group: Person-Environment Interaction in Psychopathology, Suport als Grups de Recerca – Modaliat Consolidada (SGR 2014)**

Funding Agency: Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) - Generalitat de Cataluña

Research Team: Ballespí, S. (UAB), **Cristóbal, P**. (UAB), Mitjavila, M. (UAB), Sheinbaum, T. (UAB), Vilagrà, R**.** (UAB)

Principal Investigator: Neus Barrantes-Vidal

2015-2017

Project title: **Ecological, Clinical, Psychometric and Longitudinal Trajectories Assessment of Psychosis-Proneness across the Extended Psychosis Phenotype (Evaluación Ecológica, Clínica, Psicométrica y de Trayectorias Longitudinales del Riesgo a la Psicosis en el Fenotipo Extenso de la Psicosis)**

Principal Investigator: Neus Barrantes-Vidal

Project Reference: PSI2014-54009-R

Funding Agency: Ministerio de Ciencia e Innovación, Plan Nacional de I+D+i

Duration: January 2015 to December 2017 (3 years)

Investigators: Ballespí, S. (UAB), Kwapil, T.R. (University of North Carolina at Greensboro, USA), Myin-Germeys, I. (Maastricht University, NL), Mitjavila, M. (UAB), Sheinbaum, T. (UAB). Teamwork (non doctor researchers): **P. Cristóbal** (UAB), V. Guasch, M. Montoro, S. Herrero, A. Racioppi, L. Hinojosa, M. Monsonet.

PARTICIPATION IN INTERNATIONAL MULTI-SITE PROJECT:

2012-2016

Project title: **European Network of National Schizophrenia Networks Stuying Gene-Environment Interactions (EU-GEI)**

Granting agency: European Community's Seventh Framework Programme under grant agreement No. HEALTH-F2-2010-241909 (Project EU-GEI)

General Project Coordinator: Prof. Jim van Os

UAB-SPC is a non-funded Affiliated Center of the WorkPackage 5 (Prodromal participants)

Principal Investigators: Prof. Phillip McGuire and Prof. Luccia Valmaggia (Institute of Psychiatry, London, UK)

Barcelona site coordinator: Prof. Neus Barrantes-Vidal

LANGUAGES

Catalan: Mother tongue

Spanish: Mother tongue

English: C1 Advanced

TECHNICAL SKILLS

Statistic software: SPSS, Mplus, R, HLM, Stata

Microsoft Office